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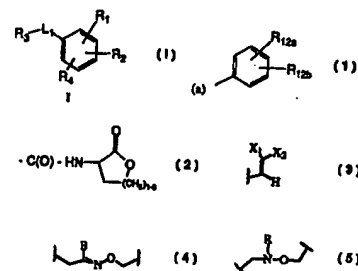
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<p>(21) International Application Number: PCT/US98/09296</p> <p>(22) International Filing Date: 7 May 1998 (07.05.98)</p> <p>(30) Priority Data: 08/852,858 7 May 1997 (07.05.97) US</p> <p>(71) Applicant: UNIVERSITY OF PITTSBURGH [US/US]; Office of Technology Transfer, 911 Williams Pitt Union, Pittsburgh, PA 15260 (US).</p> <p>(72) Inventors: SEBTI, Said, M.; 8957 Magnolia Chase Circle, Tampa, FL 33647 (US). HAMILTON, Andrew, D.; 1 White Pine Lane, Guilford, CT 06437 (US). AUGERI, David, J.; 6846 3rd Avenue, Kenosha, WI 53143 (US). BARR, Kenneth, J.; 4828 N. Hermitage #3A, Chicago, IL 60640-4143 (US). DONNER, Bernard, G.; 1901 McRae Lane, Mundelein, IL 60060 (US). FAKHOURY, Stephen, A.; 517 Buckingham, Mundelein, IL 60060 (US). JANOWICK, David, A.; 37070 Ganster Road, Beach Park, IL 60087 (US). KALVIN, Douglas, M.; 1201 Lockwood Drive, Buffalo Grove, IL 60089 (US). LARSEN,</p>		<p>John, J.; 10542 Altegld Street, Melrose Park, IL 60164 (US). LIU, Gang; 838 Alderly Lane, Gurnee, IL 60031 (US). O'CONNOR, Stephen, J.; 2103 Washington Avenue, Wilmette, IL 60091 (US). ROSENBERG, Saul, H.; 15 Lighthouse Lane, Grayslake, IL 60030 (US). SHEN, Wang; 6215 Formoor Lane, Gurnee, IL 60031 (US). SWENSON, Rolf, E.; 285 Penny Lane, Grayslake, IL 60030 (US). SORENSEN, Bryan, K.; 2620 North Lewis Avenue, Waukegan, IL 60087 (US). SULLIVAN, Gerard M.; 2214 North Sunrise Drive, Round lake Beach, Illinois 60073 (US). SZCZEPANKIEWICZ, Bruce G.; 33720 Royal Oake Lane, Apt. 209, Gages Lake, Illinois 60030 (US). TASKER, Andrew S.; 6251 Eagle Ridge Drive, Gurnee, Illinois 60031 (US). WASICK, James I.; 28440 Dorie Lane, Waterford, Wisconsin 53185 (US). WINN, Martin; 1263 Carlisle Place, Deerfield, Illinois 60015 (US).</p> <p>(74) Agents: KOKULIS, Paul, N. et al.; Cushman Darby & Cushman, Intellectual Property Group of Pillsbury Madison & Sutro, 1100 New York Avenue, N.W., Washington, DC 20005 (US).</p> <p>(81) Designated States: AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GE, GH, HU, IL, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, UZ, VN, YU, ZW, ARIPO patent (GH, GM, KE, LS, MW, SD, SZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG).</p> <p>Published <i>With international search report. Before the expiration of the time limit for amending the claims and to be republished in the event of the receipt of amendments.</i></p>

(54) Title: INHIBITORS OF PROTEIN ISOPRENYL TRANSFERASES

(57) Abstract

Compounds having formula (I) or a pharmaceutically acceptable salt thereof wherein R₁ is (a) hydrogen, (b) lower alkyl, (c) alkenyl, (d) alkoxy, (e) thioalkoxy, (f) halo, (g) haloalkyl, (h) aryl -L₂-, and (i) heterocyclic -L₂-; R₂ is selected from (a) formula (1), (b) -C(O)NH-CH(R₁₄)-C(O)OR₁₅, (c) formula (2), (d) -C(O)NH-CH(R₁₄)-C(O)NHSO₂R₁₆, (e) -C(O)NH-CH(R₁₄)-tetrazolyl, (f) -C(O)NH-heterocyclic, and (g) -C(O)NH-CH(R₁₄)-C(O)NR₁₇R₁₈; R₃ is substituted or unsubstituted heterocyclic or aryl, substituted or unsubstituted cycloalkyl or cycloalkenyl, formula (3), and -P(W)R³R³; R₄ is hydrogen, lower alkyl, haloalkyl, halogen, aryl, arylalkyl, heterocyclic, or (heterocyclic)alkyl; L₁ is absent or is selected from (a) -L₄-N(R₅)-L₅-, (b) -L₄-O-L₅-, (c) -L₄-S(O)_n-L₅-, (d) -L₄-L₆-C(W)-N(R₅)-L₅-, (e) -L₄-L₆-S(O)_m-N(R₅)-L₅-, (f) -L₄-N(R₅)-C(W)-L₇-L₅-, (g) -L₄-N(R₅)-S(O)_p-L₇-L₅-, (h) optionally substituted alkylene, (i) optionally substituted alkenylene, (j) optionally substituted alkynylene, (k) a covalent bond, (l) formula (4), and (m) formula (5) are inhibitors of protein isoprenyl transferases. Also disclosed are protein isoprenyl transferase inhibiting compositions and a method of inhibiting protein isoprenyl transferases.



(l) formula (4), and (m) formula (5) are inhibitors of protein isoprenyl transferases. Also disclosed are protein isoprenyl transferase inhibiting compositions and a method of inhibiting protein isoprenyl transferases.

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INHIBITORS OF PROTEIN ISOPRENYL TRANSFERASES

5

Technical Field

10 The present invention relates to novel compounds which are useful in inhibiting protein isoprenyl transferases (for example, protein farnesyltransferase and protein geranylgeranyltransferase) and the farnesylation or geranylgeranylation of the oncogene protein Ras and other related small g-proteins, compositions containing such compounds and methods of using such compounds.

15

Background of the Invention

Ras oncogenes are the most frequently identified activated oncogenes in human tumors. Transformed protein Ras is involved in the proliferation of cancer cells. The Ras must be farnesylated before this proliferation can occur. Farnesylation of Ras by farnesyl pyrophosphate (FPP) is effected by protein farnesyltransferase. Inhibition of protein farnesyltransferase, and thereby farnesylation of the Ras protein, blocks the ability of transformed cells to proliferate. Inhibition of protein geranylgeranyltransferase and, thereby, of geranylgeranylation of Ras proteins, also results in down regulation of Ras protein function.

25

Activation of Ras and other related small g-proteins that are farnesylated and/or geranylated also partially mediates smooth muscle cell proliferation (Circulation, I-3: 88 (1993), which is hereby incorporated herein by reference). Inhibition of protein isoprenyl transferases, and thereby farnesylation or geranylgeranylation of the Ras protein, also aids in the prevention of intimal hyperplasia associated with restenosis and atherosclerosis, a condition which compromises the success of angioplasty and surgical bypass for obstructive vascular lesions.

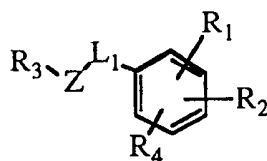
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There is therefore a need for compounds which are inhibitors of protein farnesyltransferase and protein geranylgeranyltransferase.

35

Summary of the Invention

In its principle embodiment, the invention provides a compound having the formula:



I

or a pharmaceutically acceptable salt thereof, wherein

40

R_1 is selected from the group consisting of

- (1) hydrogen,
- (2) alkenyl,
- (3) alkynyl,
- (4) alkoxy,
- 45 (5) haloalkyl,
- (6) halogen,
- (7) loweralkyl,
- (8) thioalkoxy,
- (9) aryl- L_2 - wherein aryl is selected from the group consisting of

50

- (a) phenyl,
- (b) naphthyl,
- (c) dihydronaphthyl,
- (d) tetrahydronaphthyl,
- (e) indanyl, and
- 55 (f) indenyl

wherein (a)-(f) are unsubstituted or substituted with at least one of X, Y,

or Z wherein X, Y, and Z are independently selected from the group consisting of

60

- alkenyl,
- alkynyl,
- alkoxy,
- aryl,
- carboxy,
- cyano,
- 65 halogen,
- haloalkyl,
- hydroxy,
- hydroxyalkyl,
- loweralkyl,
- 70 nitro,

N-protected amino, and
 -NRR' wherein R and R' are independently selected
 from the group consisting of
 hydrogen and
 loweralkyl,

75 oxo (=O), and
 thioalkoxy and

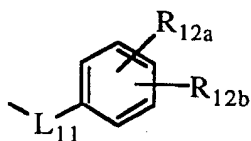
L₂ is absent or is selected from the group consisting of

80 -CH₂-,
 -CH₂CH₂-,
 -CH(CH₃)-,
 -O-,
 -C(O)-,
 -S(O)_q wherein q is 0, 1 or 2, and
 -N(R)-, and

85 (10) heterocycle-L₂- wherein L₂ is as defined above and the heterocycle is
 unsubstituted or substituted with 1, 2, 3 or 4 substituents
 independently selected from the group consisting of

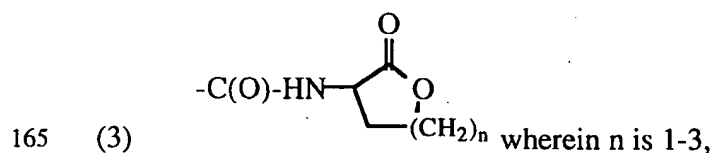
- 90 (a) loweralkyl,
 (b) hydroxy,
 (c) hydroxyalkyl,
 (d) halogen
 (e) cyano,
 (f) nitro,
 (g) oxo (=O),
 (h) -NRR',
 (i) N-protected amino,
 (j) alkoxy,
 (k) thioalkoxy,
 (l) haloalkyl,
 (m) carboxy, and
 (n) aryl;

100 R₂ is selected from the group consisting of



- 105 (1) wherein L₁₁ is selected from the group
 consisting of
 (a) a covalent bond,
 (b) -C(W)N(R)- wherein R is defined previously and W is
 selected from the group consisting of O and S,
 110 (c) -C(O)-,
 (d) -N(R)C(W)-,
 (e) -CH₂O-,
 (f) -C(O)O-, and
 (g) -CH₂N(R)-,
 115 R_{12a} is selected from the group consisting of
 (a) hydrogen,
 (b) loweralkyl, and
 (c) -C(O)OR₁₃ wherein R₁₃ is selected from the group
 consisting of
 120 hydrogen and
 a carboxy-protecting group, and
 R_{12b} is selected from the group consisting of
 (a) hydrogen and
 (b) loweralkyl,
 125 with the proviso that R_{12a} and R_{12b} are not both hydrogen,
- (2) -L₁₁-C(R₁₄)(R_v)-C(O)OR₁₅ wherein L₁₁ is defined previously,
 R_v is selected from the group consisting of
 (a) hydrogen and
 130 (b) loweralkyl,
 R₁₅ is selected from the group consisting of
 (a) hydrogen,
 (b) alkanoyloxyalkyl,
 (c) loweralkyl, and
 135 (b) a carboxy-protecting group, and
 R₁₄ is selected from the group consisting of
 (a) alkoxyalkyl,
 (b) alkoxyarylalkyl,

- 140 (c) alkoxycarbonylalkyl,
 (d) alkylsulfinylalkyl,
 (e) alkylsulfonylalkyl,
 (f) alkynyl,
 (g) aminoalkyl,
 (h) aminocarbonylalkyl,
 145 (i) aminothiocarbonylalkyl,
 (j) aryl,
 (k) arylalkyl,
 (l) carboxyalkyl,
 (m) cyanoalkyl,
 150 (n) cycloalkyl,
 (o) cycloalkylalkoxyalkyl,
 (p) cycloalkylalkyl,
 (q) (heterocyclic)alkyl,
 (r) hydroxyalkyl,
 155 (s) hydroxyarylalkyl,
 (t) loweralkyl,
 (u) sulfhydrylalkyl,
 (v) thioalkoxyalkyl wherein the thioalkoxyalkyl is
 unsubstituted or substituted with 1, 2, 3, or 4
 160 substituents selected from the group consisting of
 halogen,
 (w) thioalkoxyalkylamino, and
 (x) thiocycloalkyloxyalkyl,



- (4) $-\text{C}(=\text{O})\text{NH}-\text{CH}(\text{R}_{14})-\text{C}(=\text{O})\text{NHSO}_2\text{R}_{16}$ wherein R_{14} is defined previously
 and R_{16} is selected from the group consisting of
 170 (a) loweralkyl,
 (b) haloalkyl,
 (c) aryl wherein the aryl is unsubstituted or substituted with
 1, 2, 3, 4, or 5 substituents independently

selected from the group consisting of
loweralkyl,
hydroxy,
hydroxyalkyl,
halogen,
cyano,
nitro,
oxo (=O),
-NRR',
N-protected amino,
alkoxy,
thioalkoxy,
haloalkyl,
carboxy, and
aryl, and

- (d) heterocycle wherein the heterocycle is unsubstituted or substituted with substituents independently selected from the group consisting of
loweralkyl,
hydroxy,
hydroxyalkyl,
halogen,
cyano,
nitro,
oxo (=O),
-NRR',
N-protected amino,
alkoxy,
thioalkoxy,
haloalkyl,
carboxy, and
aryl;

(5) -C(O)NH-CH(R₁₄)-tetrazolyl wherein the tetrazole ring is unsubstituted or substituted with loweralkyl or haloalkyl,

(6) -L₁₁-heterocycle,

210

- (7) $-C(O)NH-CH(R_{14})-C(O)NR_{17}R_{18}$ wherein R_{14} is defined previously
and R_{17} and R_{18} are independently selected from the group
consisting of

215

- (a) hydrogen,
- (b) loweralkyl,
- (c) arylalkyl,
- (d) hydroxy, and
- (e) dialkylaminoalkyl,

220

- (8) $-C(O)OR_{15}$, and

- (9) $-C(O)NH-CH(R_{14})$ -heterocycle wherein R_{14} is as previously defined
and the heterocycle is unsubstituted or substituted with
loweralkyl or haloalkyl;

225

L_1 is absent or is selected from the group consisting of

- (1) $-L_4-N(R_5)-L_5-$ wherein L_4 is absent or selected from the group
consisting of

230

- (a) C_1 -to- C_{10} -alkylene and
- (b) C_2 -to- C_{16} -alkenylene,

wherein the alkylene and alkenylene groups are unsubstituted or
substituted with 1, 2, 3 or 4 substituents independently
selected from the group consisting of
alkenyl,

235

alkenyloxy,
alkenyloxyalkyl,
alkenyl[S(O)_q]alkyl,
alkoxy,

240

alkoxyalkyl wherein the alkoxyalkyl is unsubstituted or
substituted with 1 or 2 hydroxyl substituents,
with the proviso that no two hydroxyls are attached to the
same carbon,

245

alkoxycarbonyl wherein the alkoxycarbonyl is
unsubstituted or substituted with 1, 2, or 3
substituents independently selected from the
group consisting of

halogen and
cycloalkyl,
alkylsilyloxy,
250 alkyl[S(O)_q],
alkyl[S(O)_q]alkyl,
aryl wherein the aryl is unsubstituted or substituted with
1, 2, 3, 4, or 5 substituents independently
selected from the group consisting of
255 alkoxy wherein the alkoxy is unsubstituted or
substituted with substituents selected
from the group consisting of cycloalkyl,
aryl,
arylalkyl,
260 aryloxy wherein the aryloxy is unsubstituted or
substituted with 1, 2, 3, 4, or 5
substituents independently selected from
the group consisting of,
halogen,
265 nitro, and
-NRR',
cycloalkyl,
halogen,
loweralkyl,
270 hydroxyl,
nitro,
-NRR', and
-SO₂NRR',
arylalkoxy wherein the arylalkoxy is unsubstituted or
275 substituted with substituents selected from the
group consisting of alkoxy,
arylalkyl,
arylalkyl[S(O)_q]alkyl,
aryl[S(O)_q],
280 aryl[S(O)_q]alkyl wherein the aryl[S(O)_q]alkyl is
unsubstituted or substituted with 1, 2, 3, 4, or 5
substituents independently selected from
alkoxy and

loweralkyl,
285 arylalkoxyalkyl wherein the arylalkoxyalkyl is
unsubstituted or substituted with substituents
selected from the group consisting of
alkoxy, and
halogen,
290 aryloxy,
aryloxyalkyl wherein the aryloxyalkyl is unsubstituted or
substituted with substituents selected from the
group consisting of halogen,
carboxyl,
295 $-C(O)NR_C R_D$ wherein R_C and R_D are independently
selected from the group consisting of
hydrogen,
loweralkyl, and
alkoxycarbonyl or
300 R_C and R_D together with the nitrogen to which
they are attached form a ring selected
from the group consisting of
morpholine,
piperidine,
305 pyrrolidine
thiomorpholine,
thiomorpholine sulfone, and
thiomorpholine sulfoxide,
wherein the ring formed by R_C and R_D
310 together is unsubstituted or
substituted with 1 or 2
substituents independently
selected from the group consisting
of alkoxy and alkoxyalkyl,
315 cycloalkenyl wherein the cycloalkenyl is unsubstituted or
substituted with 1 or 2 substituents selected from
the group consisting of alkenyl,
cycloalkoxy,
cycloalkoxycarbonyl,
320 cycloalkoxyalkyl,

cyclolalkyl wherein the cycloalkyl is unsubstituted or
substituted with 1, 2, 3, 4, or 5 substituents
independently selected from the group consisting
of aryl,
325 loweralkyl, and
alkanoyl,
cycloalkylalkoxy,
cycloalkylalkoxycarbonyl,
cycloalkylalkoxyalkyl,
330 cycloalkylalkyl,
cyclolalkyl[S(O)_q]alkyl,
cycloalkylalkyl[S(O)_q]alkyl,
fluorenyl,
heterocycle wherein the heterocycle is unsubstituted or
335 substituted with 1, 2, 3, or 4 substituents
independently selected from the group
consisting of
alkoxy wherein the alkoxy is unsubstituted or
substituted with 1 or 2 substituents
340 independently selected from the group
consisting of aryl and cycloalkyl,
alkoxyalkyl wherein the alkoxyalkyl is
unsubstituted or substituted with 1 or 2
substituents independently selected from
345 the group consisting of
aryl and
cycloalkyl,
alkoxycarbonyl wherein the alkoxycarbonyl is
unsubstituted or substituted with 1 or 2
350 substituents independently selected from
the group consisting of
aryl and
cycloalkyl,
aryl wherein the aryl is unsubstituted or
355 substituted with 1, 2, 3, 4, or 5
substituents independently selected from
the group consisting of

360 alkanoyl,
alkoxy,
carboxaldehyde,
haloalkyl,
halogen,
loweralkyl,
nitro,
365 -NRR', and
thioalkoxy,
arylalkyl,
aryloxy,
cycloalkoxyalkyl,
370 cycloalkyl,
cycloalkylalkyl,
halogen,
heterocycle,
hydroxyl,
375 loweralkyl wherein the loweralkyl is
unsubstituted or substituted with 1, 2, or
3 substituents independently selected
from the group consisting of
heterocycle,
380 hydroxyl,
with the proviso that no two hydroxyls
are attached to the same carbon,
and
-NR^{R3}R^{R3'} wherein R^{R3} and R^{R3'} are
385 independently selected from the
group consisting of
hydrogen
aryl,
loweralkyl,
390 aryl,
arylalkyl,
heterocycle,
(heterocyclic)alkyl,
cycloalkyl, and

395 cycloalkylalkyl, and
sulfhydryl,
(heterocyclic)alkoxy,
(heterocyclic)alkyl,
(heterocyclic)alkyl[S(O)_q]alkyl,
400 (heterocyclic)oxy,
(heterocyclic)alkoxyalkyl,
(heterocyclic)oxyalkyl,
heterocycle[S(O)_q]alkyl,
hydroxyl,
405 hydroxyalkyl,
imino,
N-protected amino,
=N-O-aryl, and
=N-OH,
410 =N-O-heterocycle wherein the heterocycle is
unsubstituted or substituted with 1, 2, 3, or 4
substituents independently selected from the
group consisting of
loweralkyl,
415 hydroxy,
hydroxyalkyl,
halogen,
cyano,
nitro,
420 oxo (=O),
-NRR'
N-protected amino,
alkoxy,
thioalkoxy,
425 haloalkyl,
carboxy, and
aryl,
=N-O-loweralkyl,
-NRR³RR^{3'},
430 -NHNRC_D,
-OG wherein G is a hydroxyl protecting group,

-O-NH-R,

$\text{—O—N}=\begin{matrix} \text{J}' \\ \text{J} \end{matrix}$ wherein J and J' are independently selected

from the group consisting of

loweralkyl and

arylalkyl,

oxo,

oxyamino(alkyl)carbonylalkyl,

oxyamino(arylalkyl)carbonylalkyl,

oxyaminocarbonylalkyl,

-SO₂-A wherein A is selected from the group

consisting of

loweralkyl,

aryl, and

heterocycle

wherein the loweralkyl, aryl, and heterocycle are

unsubstituted or substituted with 1, 2, 3,

4, or 5 substituents independently

selected from the group consisting of

alkoxy,

halogen,

haloalkyl,

loweralkyl, and

nitro,

sulphydryl,

thioxo, and

thioalkoxy,

L₅ is absent or selected from the group consisting of

(a) C₁-to-C₁₀-alkylene and

(b) C₂-to-C₁₆-alkenylene

wherein (a) and (b) are unsubstituted or substituted as

defined previously, and

R₅ is selected from the group consisting of

hydrogen,

alkanoyl wherein the alkanoyl is unsubstituted or

substituted with substituents selected from the

group consisting of aryl,

alkoxy,
alkoxyalkyl,
470 alkoxycarbonyl wherein the alkoxycarbonyl is
unsubstituted or substituted with 1, 2 or 3
substituents independently selected from the
group consisting of
aryl and
475 halogen,
alkylaminocarbonylalkyl wherein the
alkylaminocarbonylalkyl is unsubstituted or
substituted with 1 or 2 substituents
independently selected from the group consisting
480 of aryl,
(anthracenyl)alkyl,
aryl,
arylalkoxy,
arylalkyl wherein the arylalkyl is unsubstituted or
485 substituted with 1, 2, 3, 4, or 5 substituents
independently selected from the group
consisting of
alkoxy,
aryl,
490 carboxyl,
cyano,
halogen,
haloalkoxy,
haloalkyl,
495 nitro,
oxo, and
-L₁₁-C(R₁₄)(R_v)-C(O)OR₁₅,
(aryl)oyl wherein the (aryl)oyl is unsubstituted or
substituted with substituents selected from the
500 group consisting of halogen,
aryloxycarbonyl,
carboxaldehyde,
-C(O)NRR',
cycloalkoxycarbonyl,

505 cycloalkylaminocarbonyl,
cycloalkylaminothiocarbonyl,
cyanoalkyl,
cycloalkyl,
cycloalkylalkyl wherein the cycloalkylalkyl is
510 unsubstituted or substituted with 1 or 2 hydroxyl
substituents,
with the proviso that no two hydroxyls are attached to the
same carbon,
(cycloalkyl)oyl,
515 (9,10-dihydroanthracenyl)alkyl wherein the
(9,10-dihydroanthracenyl)alkyl is unsubstituted
or substituted with 1 or 2 oxo substituents,
haloalkyl,
heterocycle,
520 (heterocyclic)alkyl wherein the (heterocyclic)alkyl is
unsubstituted or substituted with 1, 2, 3, 4, or 5
substituents selected from the group consisting of
loweralkyl,
(heterocyclic)oyl,
525 loweralkyl, wherein the loweralkyl is unsubstituted
or substituted with substituents selected from the
group consisting of -NRR',
-SO₂-A, and
thioalkoxyalkyl;

530

(2) -L₄-O-L₅-,(3) -L₄-S(O)_m-L₅- wherein L₄ and L₅ are defined previously and m is 0, 1,
or 2,

535

(4) -L₄-L₆-C(W)-N(R₆)-L₅- wherein L₄, W, and L₅ are defined previously,
R₆ is selected from the group consisting of

- (a) hydrogen,
- (b) loweralkyl,
- (c) aryl,
- (d) arylalkyl,

540

- (e) heterocycle,
 (f) (heterocyclic)alkyl,
 (g) cyclolakyl, and
 545 (h) cycloalkylalkyl, and
 L_6 is absent or is selected from the group consisting of
 (a) -O-,
 (b) -S-, and
 (c) -N(R₆)- wherein R₆ is selected from the group
 550 consisting of
 hydrogen,
 loweralkyl,
 aryl,
 arylalkyl,
 555 heterocycle,
 (heterocyclic)alkyl,
 cyclolakyl, and
 cycloalkylalkyl,
- 560 (5) -L₄-L₆-S(O)_m-N(R₅)-L₅-,
 (6) -L₄-L₆-N(R₅)-S(O)_m-L₅-,
 (7) -L₄-N(R₅)-C(W)-L₇-L₅- wherein L₄, R₅, W, and L₅ are
 565 defined previously and L₇ is absent or is selected from the group
 consisting of -O- and -S-,
 (8) C₁-C₁₀-alkylene wherein the alkylene group is unsubstituted or
 substituted with 1 or 2 substituents independently selected from
 570 the group consisting of
 (a) aryl,
 (b) arylalkyl,
 (c) heterocycle,
 (d) (heterocyclic)alkyl,
 575 (e) cyclolakyl,
 (f) cycloalkylalkyl,
 (g) alkylthioalkyl, and
 (h) hydroxy,

580 (9) C₂-to-C₁₀-alkenylene wherein the alkenylene group is unsubstituted or substituted with 1 or 2 substituents independently selected from the group consisting of

- (a) aryl,
- (b) arylalkyl,
- 585 (c) (aryl)oxyalkyl wherein the (aryl)oxyalkyl is unsubstituted or substituted with 1, 2, 3, 4, or 5 substituents selected from the group consisting of halogen,
- (d) heterocycle,
- 590 (e) (heterocycle)alkyl,
- (f) hydroxyalkyl,
- (g) cyclolalkyl,
- (h) cycloalkylalkyl,
- (i) alkylthioalkyl, and
- 595 (j) hydroxy,

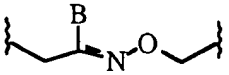
(10) C₂-to-C₁₀-alkynylene wherein the alkynylene group is unsubstituted or substituted with 1 or 2 substituents independently selected from the group consisting of

- 600 (a) aryl,
- (b) arylalkyl,
- (c) heterocycle,
- (d) (heterocyclic)alkyl,
- (e) cyclolalkyl,
- 605 (f) cycloalkylalkyl,
- (g) alkylthioalkyl, and
- (h) hydroxy,

(11) -L₄-heterocycle-L₅-,

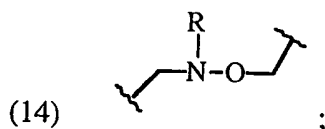
610

(12) a covalent bond,

(13)  wherein B is selected from the group consisting of loweralkyl and

615

arylalkyl, and



Z is selected from the group consisting of

- 620 (1) a covalent bond,
 (2) $-O-$,
 (3) $-S(O)_q-$, and
 (4) $-NR_Z-$ wherein R_Z is selected from the group consisting of
 625 (a) hydrogen
 (b) loweralkyl,
 (c) aryl,
 (d) arylalkyl,
 (e) heterocycle,
 (f) (heterocyclic)alkyl,
 630 (g) cyclolalkyl, and
 (h) cycloalkylalkyl;

R_3 is selected from the group consisting of

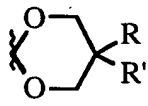
- (1) hydrogen,
 635 (2) aryl,
 (3) fluorenyl,
 (4) heterocycle,

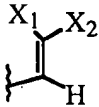
wherein (2)-(4) are unsubstituted or substituted with 1, 2, 3, 4, or 5 substituents independently selected from the group consisting of

- 640 (a) alkanoyl,
 (b) alkoxy wherein the alkoxy is unsubstituted or substituted with 1, 2, 3, 4, or 5 substituents independently selected from the group consisting of
 645 halogen,
 aryl, and
 cycloalkyl,
 (c) alkoxyalkyl wherein the alkoxyalkyl is unsubstituted or substituted with 1 or 2, 3, 4 or 5 substituents independently selected from the group consisting of

- 650 aryl and
cycloalkyl,
- (d) alkoxycarbonyl wherein the alkoxycarbonyl is unsubstituted or
substituted with 1, 2, 3, 4, or 5 substituents
independently selected from the group consisting of
- 655 aryl, and
cycloalkyl,
- (e) alkylsilyloxyalkyl,
- (f) arylalkyl,
- (g) aryl wherein the aryl is unsubstituted or substituted with 1, 2, 3,
660 4, or 5 substituents independently selected from the
group consisting of
alkanoyl,
alkoxy wherein the alkoxy is unsubstituted or substituted
with 1 or 2 substituents selected from the group
665 consisting of cycloalkyl,
carboxaldehyde,
haloalkyl,
halogen,
loweralkyl,
670 nitro,
-NRR', and
thioalkoxy,
- (h) arylalkyl,
- (i) aryloxy wherein the aryloxy is unsubstituted or
675 substituted with 1, 2, 3, 4, or 5 substituents
independently selected from the group consisting of,
halogen,
nitro, and
-NRR',
- 680 (j) (aryl)oyl,
- (k) carboxaldehyde,
- (l) carboxy,
- (m) carboxyalkyl,
- (n) -C(O)NRR" wherein R is defined previously and R" is
685 selected from the group consisting of
hydrogen,

- loweralkyl, and
carboxyalkyl,
- 690 (o) cyano,
(p) cyanoalkyl,
(q) cycloalkyl,
(r) cycloalkylalkyl,
(s) cycloalkoxyalkyl,
(t) halogen,
- 695 (u) haloalkyl wherein the haloalkyl is unsubstituted or substituted
with 1, 2, 3, 4, or 5 hydroxyl substituents,
with the proviso that no two hydroxyls are attached to the same
carbon,
- 700 (v) heterocycle,
(w) hydroxyl,
(x) hydroxyalkyl wherein the hydroxyalkyl is unsubstituted or
substituted with substituents selected from the group
consisting of aryl,
- 705 (y) loweralkyl wherein the loweralkyl is unsubstituted or substituted
with substituents selected from the group consisting of
heterocycle,
hydroxyl,
with the proviso that no two hydroxyls are attached to the
same carbon,
- 710 -NRR³RR^{3'}, and
-P(O)(OR)(OR'),
- (z) nitro,
(aa) -NRR',
(bb) oxo,
- 715 (cc) -SO₂NR_AR_B' wherein R_A' and R_B' are independently selected
from the group consisting of
hydrogen,
(aryl)oyl,
loweralkyl, and
- 720 heterocycle wherein the heterocycle is unsubstituted or
substituted with 1, 2, or 3 substituents
independently selected from the group consisting
of loweralkyl,

- (dd) sulfhydryl, and
 725 (ee) thioalkoxy,
- (5) cycloalkyl wherein the cycloalkyl is unsubstituted or substituted with
 1, 2, 3, 4 or 5 substituents selected from the group consisting of
 (a) alkoxy,
 730 (b) aryl,
 (c) arylalkoxy
 (d) aryloxy wherein the aryloxy is unsubstituted or
 substituted with 1, 2, 3, 4, or 5 substituents
 selected from the group consisting of halogen,
 735 (e) loweralkyl,
 (f) halogen,
 (g) $\text{NR}^{\text{R3}}\text{R}^{\text{R3'}}$,
 (h) oxo, and
 (i) 
 740
- (6) cycloalkenyl wherein the cycloalkenyl is unsubstituted or substituted
 with 1, 2, 3 or 4 substituents independently selected from the
 group consisting of
 (a) loweralkyl,
 745 (b) alkoxy,
 (c) halogen,
 (d) aryl,
 (e) aryloxy,
 (f) alkanoyl, and
 750 (g) $\text{NR}^{\text{R3}}\text{R}^{\text{R3'}}$,

- (7)  wherein X_1 and X_2 together are cycloalkyl wherein the
 cycloalkyl is unsubstituted or substituted with 1 or 2 substituents
 selected from the group consisting of aryl, and

755

- (8) $-\text{P}(\text{W})\text{R}^{\text{R3}}\text{R}^{\text{R3'}}$; and

R₄ is selected from the group consisting of

- 760 (1) hydrogen,
(2) loweralkyl,
(3) haloalkyl
(4) halogen,
(5) aryl,
(6) arylalkyl,
765 (7) heterocycle,
(8) (heterocyclic)alkyl
(9) alkoxy, and
(10) -NRR'; or

770 **L₁, Z, and R₃** together are selected from the group consisting of

- (1) aminoalkyl,
(1) haloalkyl,
(2) halogen,
(3) carboxaldehyde, and
775 (4) (carboxaldehyde)alkyl, and
(5) hydroxyalkyl,

with the proviso that when **L₁, Z, and R₃** together are (1)-(5), **R₁** is other than hydrogen.

In a further aspect of the present invention are disclosed pharmaceutical compositions which comprise a compound of formula I in combination with a
780 pharmaceutically acceptable carrier.

In yet another aspect of the present invention are disclosed pharmaceutical compositions which comprise a compound of formula I in combination with another chemotherapeutic agent and a pharmaceutically acceptable carrier.

In yet another aspect of the present invention is disclosed a method for inhibiting
785 protein isoprenyl transferases (i.e., protein farnesyltransferase and/or geranylgeranyltransferase) in a human or lower mammal, comprising administering to the patient a therapeutically effective amount of a compound compound of formula I.

In yet another aspect of the present invention is disclosed a method for inhibiting post-translational modification of the oncogenic Ras protein by protein farnesyltransferase,
790 protein geranylgeranyltransferase or both.

In yet another aspect of the present invention is disclosed a method for treatment of conditions mediated by farnesylated or geranylgeranylated proteins, for example, treatment of Ras associated tumors in humans and other mammals.

795 In yet another aspect of the present invention is disclosed a method for inhibiting or treating cancer in a human or lower mammal comprising administering to the patient a therapeutically effective amount of a compound of the invention alone or in combination with another chemotherapeutic agent

800 In yet another aspect of the present invention is disclosed a method for treating or preventing intimal hyperplasia associated with restenosis and atherosclerosis in a mammal comprising administering to the mammal a therapeutically effective amount of a compound of claim 1.

805 The compounds of the invention can comprise asymmetrically substituted carbon atoms. As a result, all stereoisomers of the compounds of the invention are meant to be included in the invention, including racemic mixtures, mixtures of diastereomers, as well as single diastereomers of the compounds of the invention. The terms "S" and "R" configuration, as used herein, are as defined by the IUPAC 1974 Recommendations for Section E, Fundamental Stereochemistry, Pure Appl. Chem. (1976) 45, 13-30, which is hereby incorporated herein by reference.

810

Detailed Description

Definitions of Terms

815 As used herein the terms "Cys," "Glu," "Leu," "Lys," "Met," "nor-Leu," "nor-Val," "Phe," "Ser" and "Val" refer to cysteine, glutamine, leucine, lysine, methionine, norleucine, norvaline, phenylalanine, serine and valine in their L-, D- or DL forms. As used herein these amino acids are in their naturally occurring L- form.

820 As used herein, the term "carboxy protecting group" refers to a carboxylic acid protecting ester group employed to block or protect the carboxylic acid functionality while the reactions involving other functional sites of the compound are carried out. Carboxy protecting groups are disclosed in Greene, "Protective Groups in Organic Synthesis" pp. 152-186 (1981), which is hereby incorporated herein by reference. In addition, a carboxy protecting group can be used as a prodrug whereby the carboxy protecting group can be readily cleaved *in vivo* (for example by enzymatic hydrolysis) to release the biologically active parent. T. Higuchi and V. Stella provide a thorough discussion of the prodrug concept in "Pro-drugs as Novel Delivery Systems", Vol 14 of the A.C.S. Symposium Series, American Chemical Society (1975), which is hereby incorporated herein by reference. Such carboxy protecting groups are well known to those skilled in the art, having been extensively used in the protection of carboxyl groups in the penicillin and cephalosporin fields (as described in U.S. Pat. No. 3,840,556 and 3,719,667, the disclosures of which are hereby incorporated herein by reference). Examples of esters 830 useful as prodrugs for compounds containing carboxyl groups can be found on pages 14-21

of "Bioreversible Carriers in Drug Design: Theory and Application", edited by E.B. Roche, Pergamon Press, New York (1987), which is hereby incorporated herein by reference. Representative carboxy protecting groups are C₁ to C₈ loweralkyl (e.g., methyl, ethyl or tertiary butyl and the like); arylalkyl, for example, phenethyl or benzyl and substituted derivatives thereof such as alkoxybenzyl or nitrobenzyl groups and the like; arylalkenyl, for example, phenylethenyl and the like; aryl and substituted derivatives thereof, for example, 5-indanyl and the like; dialkylaminoalkyl (e.g., dimethylaminoethyl and the like); alkanoyloxyalkyl groups such as acetoxymethyl, butyryloxymethyl, valeryloxymethyl, isobutyryloxymethyl, isovaleryloxymethyl, 1-(propionyloxy)-1-ethyl, 1-(pivaloyloxy)-1-ethyl, 1-methyl-1-(propionyloxy)-1-ethyl, pivaloyloxymethyl, propionyloxymethyl and the like; cycloalkanoyloxyalkyl groups such as cyclopropylcarbonyloxymethyl, cyclobutylcarbonyloxymethyl, cyclopentylcarbonyloxymethyl, cyclohexylcarbonyloxymethyl and the like; aroyloxyalkyl, such as benzoyloxymethyl, benzoyloxyethyl and the like; arylalkylcarbonyloxyalkyl, such as benzylcarbonyloxymethyl, 2-benzylcarbonyloxyethyl and the like; alkoxycarbonylalkyl or cycloalkyloxycarbonylalkyl, such as methoxycarbonylmethyl, cyclohexyloxycarbonylmethyl, 1-methoxycarbonyl-1-ethyl, and the like; alkoxycarbonyloxyalkyl or cycloalkyloxycarbonyloxyalkyl, such as methoxycarbonyloxymethyl, t-butyloxycarbonyloxymethyl, 1-ethoxycarbonyloxy-1-ethyl, 1-cyclohexyloxycarbonyloxy-1-ethyl and the like; aryloxycarbonyloxyalkyl, such as 2-(phenoxy carbonyloxy)ethyl, 2-(5-indanyloxycarbonyloxy)ethyl and the like; alkoxyalkylcarbonyloxyalkyl, such as 2-(1-methoxy-2-methylpropan-2-oyloxy)ethyl and the like; arylalkyloxycarbonyloxyalkyl, such as 2-(benzyloxycarbonyloxy)ethyl and the like; arylalkenyloxycarbonyloxyalkyl, such as 2-(3-phenylpropen-2-yloxycarbonyloxy)ethyl and the like; alkoxycarbonylaminoalkyl, such as t-butyloxycarbonylaminomethyl and the like; alkylaminocarbonylaminoalkyl, such as methylaminocarbonylaminomethyl and the like; alkanoylaminoalkyl, such as acetylaminomethyl and the like; heterocycliccarbonyloxyalkyl, such as 4-methylpiperazinylcarbonyloxymethyl and the like; dialkylaminocarbonylalkyl, such as dimethylaminocarbonylmethyl, diethylaminocarbonylmethyl and the like; (5-(loweralkyl)-2-oxo-1,3-dioxolen-4-yl)alkyl, such as (5-t-butyl-2-oxo-1,3-dioxolen-4-yl)methyl and the like; and (5-phenyl-2-oxo-1,3-dioxolen-4-yl)alkyl, such as (5-phenyl-2-oxo-1,3-dioxolen-4-yl)methyl and the like.

Preferred carboxy-protected compounds of the invention are compounds wherein the protected carboxy group is a loweralkyl, cycloalkyl or arylalkyl ester, for example, methyl ester, ethyl ester, propyl ester, isopropyl ester, butyl ester, sec-butyl ester, isobutyl ester, amyl ester, isoamyl ester, octyl ester, cyclohexyl ester, phenylethyl ester and the like or an

alkanoyloxyalkyl, cycloalkanoyloxyalkyl, aroyloxyalkyl or an arylalkylcarbonyloxyalkyl ester.

The term "N-protecting group" or "N-protected" as used herein refers to those groups intended to protect the N-terminus of an amino acid or peptide or to protect an amino group against undesirable reactions during synthetic procedures. Commonly used N-protecting groups are disclosed in Greene, "Protective Groups In Organic Synthesis," (John Wiley & Sons, New York (1981)), which is hereby incorporated herein by reference. N-protecting groups comprise acyl groups such as formyl, acetyl, propionyl, pivaloyl, t-butylacetyl, 2-chloroacetyl, 2-bromoacetyl, trifluoroacetyl, trichloroacetyl, phthalyl, o-nitrophenoxyacetyl, a-chlorobutyryl, benzoyl, 4-chlorobenzoyl, 4-bromobenzoyl, 4-nitrobenzoyl, and the like; sulfonyl groups such as benzenesulfonyl, p-toluenesulfonyl and the like; carbamate forming groups such as benzyloxycarbonyl, p-chlorobenzyloxycarbonyl, p-methoxybenzyloxycarbonyl, p-nitrobenzyloxycarbonyl, 2-nitrobenzyloxycarbonyl, p-bromobenzyloxycarbonyl, 3,4-dimethoxybenzyloxycarbonyl, 3,5-dimethoxybenzyloxycarbonyl, 2,4-dimethoxybenzyloxycarbonyl, 4-methoxybenzyloxycarbonyl, 2-nitro-4,5-dimethoxybenzyloxycarbonyl, 3,4,5-trimethoxybenzyloxycarbonyl, 1-(p-biphenyl)-1-methylethoxycarbonyl, a,a-dimethyl-3,5-dimethoxybenzyloxycarbonyl, benzhydryloxycarbonyl, t-butyloxycarbonyl, diisopropylmethoxycarbonyl, isopropylloxycarbonyl, ethoxycarbonyl, methoxycarbonyl, allyloxycarbonyl, 2,2,2-trichloroethoxycarbonyl, phenoxycarbonyl, 4-nitrophenoxycarbonyl, fluorenyl-9-methoxycarbonyl, cyclopentylloxycarbonyl, adamantylloxycarbonyl, cyclohexylloxycarbonyl, phenylthiocarbonyl and the like; alkyl groups such as benzyl, triphenylmethyl, benzyloxymethyl and the like; and silyl groups such as trimethylsilyl and the like. Preferred N-protecting groups are formyl, acetyl, benzoyl, pivaloyl, t-butylacetyl, phenylsulfonyl, benzyl, t-butyloxycarbonyl (Boc) and benzyloxycarbonyl (Cbz).

The term "alkanoyl" as used herein refers to $R_{29}C(O)-$ wherein R_{29} is a loweralkyl group. The alkanoyl groups of this invention can be optionally substituted.

The term "alkanoylaminoalkyl" as used herein refers to a loweralkyl radical to which is appended $R_{71}-NH-$ wherein R_{71} is an alkanoyl group. The alkanoylaminoalkyl groups of this invention can be optionally substituted.

The term "alkanoyloxy" as used herein refers to $R_{29}C(O)-O-$ wherein R_{29} is a loweralkyl group. The alkanoyloxy groups of this invention can be optionally substituted.

The term "alkanoyloxyalkyl" as used herein refers to a loweralkyl radical to which is appended an alkanoyloxy group. The alkanoyloxyalkyl groups of this invention can be optionally substituted.

The term "alkenyl" as used herein refers to a straight or branched chain hydrocarbon containing from 2 to 10 carbon atoms and also containing at least one carbon-carbon double bond. Examples of alkenyl include $-\text{CH}=\text{CH}_2$, $-\text{CH}_2\text{CH}=\text{CH}_2$, $-\text{C}(\text{CH}_3)=\text{CH}_2$, $-\text{CH}_2\text{CH}=\text{CHCH}_3$, and the like. The alkenyl groups of this invention can be optionally substituted.

The term "alkenylene" as used herein refers to a divalent group derived from a straight or branched chain hydrocarbon containing from 2 to 20 carbon atoms and also containing at least one carbon-carbon double bond. Examples of alkenylene include $-\text{CH}=\text{CH}-$, $-\text{CH}_2\text{CH}=\text{CH}-$, $-\text{C}(\text{CH}_3)=\text{CH}-$, $-\text{CH}_2\text{CH}=\text{CHCH}_2-$, and the like. The alkenylene groups of this invention can be optionally substituted.

The term "alkenyloxy" as used herein refers to an alkenyl group attached to the parent molecular group through an oxygen atom. The alkenyloxy groups of this invention can be optionally substituted.

The term "alkenyloxyalkyl" as used herein refers to a loweralkyl group to which is attached an alkenyloxy group. The alkenyloxyalkyl groups of this invention can be optionally substituted.

The term "alkoxy" as used herein refers to $\text{R}_{30}\text{O}-$ wherein R_{30} is loweralkyl as defined above. Representative examples of alkoxy groups include methoxy, ethoxy, t-butoxy and the like. The alkoxy groups of this invention can be optionally substituted.

The term "alkoxyalkyl" as used herein refers to a loweralkyl group to which is attached an alkoxy group. The alkoxyalkyl groups of this invention can be optionally substituted.

The term "alkoxyalkoxy" as used herein refers to $\text{R}_{31}\text{O}-\text{R}_{32}\text{O}-$ wherein R_{31} is loweralkyl as defined above and R_{32} is an alkylene radical. Representative examples of alkoxyalkoxy groups include methoxymethoxy, ethoxymethoxy, t-butoxymethoxy and the like. The alkoxyalkoxy groups of this invention can be optionally substituted.

The term "alkoxyalkyl" as used herein refers to an alkoxy group as previously defined appended to an alkyl group as previously defined. Examples of alkoxyalkyl include, but are not limited to, methoxymethyl, methoxyethyl, isopropoxymethyl and the like. The alkoxyalkyl groups of this invention can be optionally substituted.

The term "alkoxyalkylcarbonyloxyalkyl" as used herein refers to a loweralkyl radical to which is appended $\text{R}_{66}-\text{C}(\text{O})-\text{O}-$ wherein R_{66} is an alkoxyalkyl group.

The term "alkoxyarylalkyl" as used herein refers to an arylalkyl group to which is attached an alkoxy group. The alkoxyarylalkyl groups of this invention can be optionally substituted.

The term "alkoxycarbonyl" as used herein refers to an alkoxy group as previously defined appended to the parent molecular moiety through a carbonyl group. Examples of

940 alkoxy carbonyl include methoxycarbonyl, ethoxycarbonyl, isopropoxycarbonyl and the like. The alkoxy carbonyl groups of this invention can be optionally substituted. The alkoxy carbonyl groups of this invention can be optionally substituted.

The term "alkoxy carbonyl alkyl" as used herein refers to an alkoxy carbonyl group as previously defined appended to a lower alkyl radical. Examples of alkoxy carbonyl alkyl
945 include methoxycarbonylmethyl, 2-ethoxycarbonylethyl and the like. The alkoxy carbonyl alkyl groups of this invention can be optionally substituted.

The term "alkoxy carbonyl amino alkyl" as used herein refers to a lower alkyl radical to which is appended $R_{69}-NH-$ wherein R_{69} is an alkoxy carbonyl group. The alkoxy carbonyl amino alkyl groups of this invention can be optionally substituted.

950 The term "alkoxy carbonyl oxy alkyl" as used herein refers to a lower alkyl radical to which is appended $R_{63}-O-$ wherein R_{63} is an alkoxy carbonyl group. The alkoxy carbonyl oxy alkyl groups of this invention can be optionally substituted.

The term "alkyl amino" as used herein refers to $R_{35}NH-$ wherein R_{35} is a lower alkyl group, for example, methyl amino, ethyl amino, butyl amino, and the like. The alkyl amino
955 groups of this invention can be optionally substituted.

The term "alkyl amino alkyl" as used herein refers to a lower alkyl radical to which is appended an alkyl amino group. The alkyl amino alkyl groups of this invention can be optionally substituted.

The term "alkyl aminocarbonyl amino alkyl" as used herein refers to a lower alkyl
960 radical to which is appended $R_{70}-C(O)-NH-$ wherein R_{70} is an alkyl amino group. The alkyl aminocarbonyl amino alkyl groups of this invention can be optionally substituted.

The term "alkylene" as used herein refers to a divalent group derived from a straight or branched chain saturated hydrocarbon having from 1 to 10 carbon atoms by the removal of two hydrogen atoms, for example methylene, 1,2-ethylene, 1,1-ethylene, 1,3-propylene,
965 2,2-dimethylpropylene, and the like. The alkylene groups of this invention can be optionally substituted.

The term "alkyl silyloxy" as used herein refers to a lower alkyl group to which is attached $-OSiR_W R_X R_Y$ wherein R_W , R_X , and R_Y are selected from the group consisting of lower alkyl.

970 The term "alkyl sulfinyl" as used herein refers to $R_{33}S(O)-$ wherein R_{33} is a lower alkyl group. The alkyl sulfinyl groups of this invention can be optionally substituted.

The term "alkyl sulfinyl alkyl" as used herein refers to an alkyl group to which is attached a alkyl sulfinyl group. The alkyl sulfinyl alkyl groups of this invention can be optionally substituted.

975 The term "alkyl sulfonyl" as used herein refers to $R_{34}S(O)_2-$ wherein R_{34} is a lower alkyl group. The alkyl sulfonyl groups of this invention can be optionally substituted.

The term "alkylsulfonylalkyl" as used herein refers to a loweralkyl radical to which is appended an alkylsulfonyl group. The alkylsulfonylalkyl groups of this invention can be optionally substituted.

980 The term alkylthioalkyl as used herein refers to a lower alkyl group as defined herein attached to the parent molecular moiety through a sulfur atom and an alkylene group. The alkylthioalkyl groups of this invention can be optionally substituted.

The term "alkynyl" as used herein refers to a straight or branched chain hydrocarbon containing from 2 to 10 carbon atoms and also containing at least one carbon-carbon triple bond. Examples of alkynyl include $-C\equiv CH$, $-CH_2C\equiv CH$, $-CH_2C\equiv CCH_3$, and the like. 985 The alkynyl groups of this invention can be optionally substituted.

The term "alkynylene" as used herein refers to a divalent group derived from a straight or branched chain hydrocarbon containing from 2 to 10 carbon atoms and also containing at least one carbon-carbon triple bond. Examples of alkynylene include $-C\equiv C-$, 990 $-CH_2C\equiv C-$, $-CH_2C\equiv CCH_2-$, and the like. The alkynylene groups of this invention can be optionally substituted.

The term "amino" as used herein refers to $-NH_2$.

The term "aminocarbonyl" as used herein refers to an amino group attached to the parent molecular group through a carbonyl group. The aminocarbonyl groups of this 995 invention can be optionally substituted.

The term "aminocarbonylalkyl" as used herein refers to an alkyl group to which is attached an aminocarbonyl group. The aminocarbonylalkyl groups of this invention can be optionally substituted.

1000 The term "aminoalkyl" as used herein refers to a loweralkyl radical to which is appended an amino group. The aminoalkyl groups of this invention can be optionally substituted.

The term "aminothiocarbonyl" as used herein refers to an amino group attached to the parent molecular group through a thiocarbonylcarbonyl ($C=S$) group. The aminothiocarbonyl groups of this invention can be optionally substituted.

1005 The term "aryloxyalkyl" as used herein refers to a loweralkyl radical to which is appended an aryloxy group (i.e., $R_{61}-C(O)O-$ wherein R_{61} is an aryl group). The aryloxyalkyl groups of this invention can be optionally substituted.

The term "aryl" as used herein refers to a mono- or bicyclic carbocyclic ring system having one or two aromatic rings including, but not limited to, phenyl, naphthyl, 1010 tetrahydronaphthyl, indanyl, indenyl and the like. Aryl groups (including bicyclic aryl groups) can be unsubstituted or substituted with one, two or three substituents independently selected from loweralkyl, haloalkyl, alkoxy, thioalkoxy, amino, alkylamino, dialkylamino, hydroxy, halo, mercapto, sulfhydryl, nitro, cyano, carboxaldehyde, carboxy,

alkoxycarbonyl, haloalkyl-C(O)-NH-, haloalkenyl-C(O)-NH- and carboxamide. In addition, substituted aryl groups include tetrafluorophenyl and pentafluorophenyl.

The term "arylalkenyl" as used herein refers to an alkenyl radical to which is appended an aryl group. The arylalkenyl groups of this invention can be optionally substituted.

The term "arylalkenyloxycarbonyloxyalkyl" as used herein refers to a loweralkyl radical to which is appended $R_{68}-O-C(O)-O-$ wherein R_{68} is an arylalkenyl group. The arylalkenyloxycarbonyloxyalkyl groups of this invention can be optionally substituted.

The term "arylalkoxy" as used herein refers to an alkoxy group to which is attached an aryl group. The arylalkoxy groups of this invention can be optionally substituted.

The term "arylalkyl" as used herein refers to a loweralkyl radical to which is appended an aryl group. Representative arylalkyl groups include benzyl, phenylethyl, hydroxybenzyl, fluorobenzyl, fluorophenylethyl and the like. The arylalkyl groups of this invention can be optionally substituted.

The term "arylalkylcarbonyloxyalkyl" as used herein refers to a loweralkyl radical to which is appended an arylalkylcarbonyloxy group (i.e., $R_{62}C(O)O-$ wherein R_{62} is an arylalkyl group). The arylalkylcarbonyloxyalkyl groups of this invention can be optionally substituted.

The term "aryloxy" as used herein refers to an aryl group attached to the parent molecular group through an oxygen atom. The aryloxy groups of this invention can be optionally substituted.

The term "aryloxy carbonyl" as used herein refers to an aryloxy group attached to the parent molecular group through a carbonyl group. The aryloxy carbonyl groups of this invention can be optionally substituted.

The term "aryloyl" as used herein refers to an aryl group attached to the parent molecular group through a carbonyl group. The aryloyl groups of this invention can be optionally substituted.

The term "arylalkyloxycarbonyloxyalkyl" as used herein refers to a loweralkyl radical to which is appended $R_{67}-O-C(O)-O-$ wherein R_{67} is an arylalkyl group. The arylalkyloxycarbonyloxyalkyl groups of this invention can be optionally substituted.

The term "aryloxyalkyl" as used herein refers to a loweralkyl radical to which is appended $R_{65}-O-$ wherein R_{65} is an aryl group. The aryloxyalkyl groups of this invention can be optionally substituted.

The term "arylalkoxy" as used herein refers to an alkoxy radical to which is appended $R_{65}-O-$ wherein R_{65} is an aryl group. The arylalkoxy groups of this invention can be optionally substituted.

1050 The term "arylalkyloxyalkyl" as used herein refers to a loweralkyl radical to which is appended an arylalkoxy group. The arylalkyloxyalkyl groups of this invention can be optionally substituted.

The term "aryloxy" as used herein refers to $R_{65}-O-$ wherein R_{65} is an aryl group. The aryloxy groups of this invention can be optionally substituted. The aryloxy groups of 1055 this invention can be optionally substituted.

The term "(aryl)oyl" as used herein refers to an aryl group attached to the parent molecular group through a carbonyl group. The (aryl)oyl groups of this invention can be optionally substituted.

The term "aryloxythioalkoxyalkyl" as used herein refers to a loweralkyl radical to 1060 which is appended $R_{75}-S-$ wherein R_{75} is an aryloxyalkyl group. The aryloxythioalkoxyalkyl groups of this invention can be optionally substituted.

The term "aryloxycarbonyloxyalkyl" as used herein refers to a loweralkyl radical to which is appended $R_{65}-O-C(O)-O-$ wherein R_{65} is an aryl group. The 1065 aryloxycarbonyloxyalkyl groups of this invention can be optionally substituted.

The term "arylsulfonyl" as used herein refers to $R_{36}S(O)_2-$ wherein R_{36} is an aryl group. The arylsulfonyl groups of this invention can be optionally substituted.

The term "arylsulfonyloxy" as used herein refers to $R_{37}S(O)_2O-$ wherein R_{37} is an aryl group. The arylsulfonyloxy groups of this invention can be optionally substituted.

The term "carboxy" as used herein refers to $-COOH$.

1070 The term "carboxyalkyl" as used herein refers to a loweralkyl radical to which is appended a carboxy ($-COOH$) group. The carboxyalkyl groups of this invention can be optionally substituted.

The term "cyanoalkyl" as used herein used herein refers to a loweralkyl radical to which is appended a cyano ($-CN$) group. The cyanoalkyl groups of this invention can be 1075 optionally substituted.

The term "carboxaldehyde" as used herein used herein refers to $-CHO$.

The term "(carboxaldehyde)alkyl" as used herein used herein refers to a carboxaldehyde group attached to a loweralkyl group. The (carboxaldehyde)alkyl groups of this invention can be optionally substituted.

1080 The terms "cycloalkanoyl" and "(cycloalkyl)oyl" refer to a cycloalkyl group attached to the parent molecular group through a carbonyl group. The cycloalkanoyl and (cycloalkyl)oyl groups of this invention can be optionally substituted.

The term "cycloalkanoylalkyl" as used herein refers to a loweralkyl radical to which is appended a cycloalkanoyl group (i.e., $R_{60}-C(O)-$ wherein R_{60} is a cycloalkyl group).

1085 The cycloalkanoylalkyl groups of this invention can be optionally substituted.

The term "cycloalkylalkoxyalkyl" as used herein refers to an alkoxyalkyl group to which is attached a cycloalkyl group. The cycloalkylalkoxyalkyl groups of this invention can be optionally substituted.

1090 The term "cycloalkenyl" as used herein refers to an alicyclic group comprising from 3 to 10 carbon atoms and containing a carbon-carbon double bond including, but not limited to, cyclopentenyl, cyclohexenyl and the like. The cycloalkenyl groups of this invention can be optionally substituted.

1095 The term "cycloalkoxy" as used herein refers to a cycloalkyl group attached to the parent molecular group through an oxygen atom. The cycloalkoxy groups of this invention can be optionally substituted.

The term "cycloalkoxyalkyl" as used herein refers to a loweralkyl group to which is attached a cycloalkoxy group. The cycloalkoxyalkyl groups of this invention can be optionally substituted.

1100 The term "cycloalkoxycarbonyl" as used herein refers to a cycloalkoxy group attached to the parent molecular group through a carbonyl group. The cycloalkoxycarbonyl groups of this invention can be optionally substituted.

1105 The term "cycloalkyl" as used herein refers to an alicyclic group comprising from 3 to 10 carbon atoms including, but not limited to, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, norbornyl, adamantyl and the like. The cycloalkyl groups of this invention can be optionally substituted. The cycloalkyl groups of this invention can be optionally substituted.

The term "cycloalkylaminocarbonyl" as used herein refers to $\text{NHR}_{60}\text{C}(\text{O})-$ wherein R_{60} is a cycloalkyl group. The cycloalkylaminocarbonyl groups of this invention can be optionally substituted.

1110 The term "cycloalkylaminothiocarbonyl" as used herein refers to $\text{NHR}_{60}\text{C}(\text{S})-$ wherein R_{60} is defined above. The cycloalkylaminothiocarbonyl groups of this invention can be optionally substituted.

1115 The term "cycloalkylalkoxy" as used herein refers to an alkoxy radical to which is appended a cycloalkyl group. The cycloalkylalkoxy groups of this invention can be optionally substituted.

The term "cycloalkylalkoxyalkyl" as used herein refers to an alkyl radical to which is appended a cycloalkylalkoxy group. The cycloalkylalkoxyalkyl groups of this invention can be optionally substituted.

1120 The term "cycloalkylalkoxycarbonyl" as used herein refers to a cycloalkylalkoxy radical attached to the parent molecular group through a carbonyl group. The cycloalkylalkoxycarbonyl groups of this invention can be optionally substituted.

The term "cycloalkylalkyl" as used herein refers to a loweralkyl radical to which is appended a cycloalkyl group. Representative examples of cycloalkylalkyl include cyclopropylmethyl, cyclohexylmethyl, 2-(cyclopropyl)ethyl, adamantylmethyl and the like.

1125 The cycloalkylalkyl groups of this invention can be optionally substituted.

The term "cycloalkyloxycarbonyloxyalkyl" as used herein refers to a loweralkyl radical to which is appended $R_{64}-O-C(O)-O-$ wherein R_{64} is a cycloalkyl group. The cycloalkyloxycarbonyloxyalkyl groups of this invention can be optionally substituted.

1130 The term "dialkoxyalkyl" as used herein refers to a loweralkyl radical to which is appended two alkoxy groups. The dialkoxyalkyl groups of this invention can be optionally substituted.

1135 The term "dialkylamino" as used herein refers to $R_{38}R_{39}N-$ wherein R_{38} and R_{39} are independently selected from loweralkyl, for example dimethylamino, diethylamino, methyl propylamino, and the like. The dialkylamino groups of this invention can be optionally substituted.

The term "dialkylaminoalkyl" as used herein refers to a loweralkyl radical to which is appended a dialkylamino group. The dialkylaminoalkyl groups of this invention can be optionally substituted.

1140 The term "dialkylaminocarbonylalkyl" as used herein refers to a loweralkyl radical to which is appended $R_{73}-C(O)-$ wherein R_{73} is a dialkylamino group. The dialkylaminocarbonylalkyl groups of this invention can be optionally substituted.

The term "dioxoalkyl" as used herein refers to a loweralkyl radical which is substituted with two oxo ($=O$) groups. The dioxoalkyl groups of this invention can be optionally substituted.

1145 The term "dithioalkoxyalkyl" as used herein refers to a loweralkyl radical to which is appended two thioalkoxy groups. The dithioalkoxyalkyl groups of this invention can be optionally substituted.

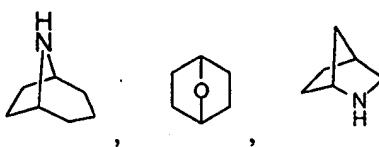
The term "halogen" or "halo" as used herein refers to I, Br, Cl or F.

1150 The term "haloalkenyl" as used herein refers to an alkenyl radical, as defined above, bearing at least one halogen substituent. The haloalkenyl groups of this invention can be optionally substituted.

1155 The term "haloalkyl" as used herein refers to a lower alkyl radical, as defined above, bearing at least one halogen substituent, for example, chloromethyl, fluoroethyl or trifluoromethyl and the like. Haloalkyl can also include perfluoroalkyl wherein all hydrogens of a loweralkyl group are replaced with fluorides.

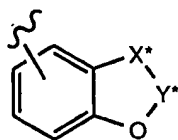
The term "heterocyclic ring" or "heterocyclic" or "heterocycle" as used herein refers to a 5-, 6- or 7-membered ring containing one, two or three heteroatoms independently selected from the group consisting of nitrogen, oxygen and sulfur or a 5-membered ring

containing 4 nitrogen atoms; and includes a 5-, 6- or 7-membered ring containing one, two
 1160 or three nitrogen atoms; one oxygen atom; one sulfur atom; one nitrogen and one sulfur
 atom; one nitrogen and one oxygen atom; two oxygen atoms in non-adjacent positions; one
 oxygen and one sulfur atom in non-adjacent positions; two sulfur atoms in non-adjacent
 positions; two sulfur atoms in adjacent positions and one nitrogen atom; two adjacent
 nitrogen atoms and one sulfur atom; two non-adjacent nitrogen atoms and one sulfur atom;
 1165 two non-adjacent nitrogen atoms and one oxygen atom. The 5-membered ring has 0-2
 double bonds and the 6- and 7-membered rings have 0-3 double bonds. The term
 "heterocyclic" also includes bicyclic, tricyclic and tetracyclic groups in which any of the
 above heterocyclic rings is fused to one or two rings independently selected from the group
 consisting of an aryl ring, a cyclohexane ring, a cyclohexene ring, a cyclopentane ring, a
 1170 cyclopentene ring and another monocyclic heterocyclic ring (for example, indolyl, quinolyl,
 isoquinolyl, tetrahydroquinolyl, benzofuryl or benzothienyl and the like). Heterocyclics
 include: pyrrolyl, pyrrolinyl, pyrrolidinyl, pyrazolyl, pyrazolinyl, pyrazolidinyl,
 imidazolyl, imidazoliny, imidazolidinyl, pyridyl, piperidinyl, homopiperidinyl, pyrazinyl,
 piperazinyl, pyrimidinyl, pyridazinyl, oxazolyl, oxazolidinyl, isoxazolyl, isoxazolidinyl,
 1175 morpholinyl, thiomorpholinyl, thiazolyl, thiazolidinyl, isothiazolyl, isothiazolidinyl,
 indolyl, quinoliny, isoquinoliny, benzimidazolyl, benzothiazolyl, benzoxazolyl, furyl,
 thienyl, thiazolidinyl, isothiazolyl, triazolyl, tetrazolyl, oxadiazolyl, thiadiazolyl, pyrimidyl,
 tetrahydrofuranyl, dihydrofuranyl, tetrahydrothienyl, dihydrothienyl, dihydroindolyl,
 tetrahydroquinolyl, tetrahydroisoquinolyl, pyranyl, dihydropyranyl, dithiazolyl,
 1180 benzofuranyl and benzothienyl. Heterocyclics also include bridged bicyclic groups wherein
 a monocyclic heterocyclic group is bridged by an alkylene group, for example,



and the like.

1185 Heterocyclics also include compounds of the formula



wherein X* is -CH₂-, -CH₂O- or -O- and Y* is -C(O)- or -(C(R''))_v - wherein R'' is
 hydrogen or C₁-C₄-alkyl and v is 1, 2 or 3 such as 1,3-benzodioxolyl, 1,4-benzodioxanyl
 and the like.

- 1190 Heterocyclics can be unsubstituted or substituted with one, two, three, four or five substituents independently selected from the group consisting of
- a) hydroxy, b) -SH, c) halo, d) oxo (=O), e) thioxo (=S), f) amino, g) -NHOH, h) alkylamino, i) dialkylamino, j) alkoxy, k) alkoxyalkoxy, l) haloalkyl, m) hydroxyalkyl, n) alkoxyalkyl, o) cycloalkyl which is unsubstituted or substituted with one, two, three or four
- 1195 loweralkyl groups, p) cycloalkenyl which is unsubstituted or substituted with one, two, three or four loweralkyl groups, q) alkenyl, r) alkynyl, s) aryl, t) arylalkyl, u) -COOH, v) -SO₃H, w) loweralkyl, x) alkoxycarbonyl, y) -C(O)NH₂, z) -C(S)NH₂, aa) -C(=N-OH)NH₂, bb) aryl-L₁₆-C(O)- wherein L₁₆ is an alkenylene radical, cc) -S-L₁₇-C(O)OR₄₀ wherein L₁₇ is an alkylene radical which is unsubstituted or substituted with one or two
- 1200 substituents independently selected from the group consisting of alkanoyl, oxo (=O) or methinylamino (=CHNR₄₁R₄₂ wherein R₄₁ is hydrogen or loweralkyl and R₄₂ is loweralkyl) and R₄₀ is hydrogen or a carboxy-protecting group, dd) -S-L₁₈-C(O)NR₄₃R₄₄ wherein L₁₈ is an alkylene radical which is unsubstituted or substituted with one or two
- 1205 substituents independently selected from the group consisting of alkanoyl, oxo (=O) or methinylamino (=CHNR₄₁R₄₂ wherein R₄₁ is hydrogen or loweralkyl and R₄₃ and R₄₄ are independently selected from the group consisting of hydrogen, loweralkyl and aryl, ee) -S-L₁₉-CN wherein L₁₉ is an alkylene radical, ff) -S-L₂₀-R₄₅ wherein L₂₀ is absent or is an alkylene radical or an alkenylene radical or an alkynylene radical wherein the alkylene, alkenylene or alkynylene radical is unsubstituted or substituted with oxo (=O) and R₄₅ is
- 1210 hydrogen, aryl, arylalkyl or heterocyclic wherein the heterocyclic is unsubstituted or substituted with one, two or three substituents independently selected from the group consisting of loweralkyl, hydroxy, hydroxyalkyl, halo, nitro, oxo (=O), amino, N-protected amino, alkoxy, thioalkoxy and haloalkyl, gg) -O-L₂₁-R₄₆ wherein L₂₁ is absent or is an alkylene radical or an alkenylene radical or an alkynylene radical wherein the
- 1215 alkylene, alkenylene or alkynylene radical is unsubstituted or substituted with one or two substituents independently selected from the group consisting of alkanoyl, oxo (=O) or methinylamino (=CHNR₄₁R₄₂ wherein R₄₁ is hydrogen or loweralkyl and R₄₆ is hydrogen, aryl, arylalkyl or heterocyclic wherein the heterocyclic is unsubstituted or substituted with one, two or three substituents independently selected from the group
- 1220 consisting of loweralkyl, hydroxy, hydroxyalkyl, halo, nitro, oxo (=O), amino, N-protected amino, alkoxy, thioalkoxy and haloalkyl, hh) -O-S(O)₂-R₄₇ wherein R₄₇ is aryl, arylalkyl, heterocyclic or heterocyclicalkyl wherein the heterocyclic is unsubstituted or substituted with one, two or three substituents independently selected from the group consisting of loweralkyl, hydroxy, hydroxyalkyl, halo, nitro, oxo (=O), amino, N-protected amino, alkoxy, thioalkoxy and haloalkyl, ii) -S(O)₂-NH-R₄₈ wherein R₄₈ is
- 1225 aryl, arylalkyl, heterocyclic or heterocyclicalkyl wherein the heterocyclic is unsubstituted or

substituted with one, two or three substituents independently selected from the group consisting of loweralkyl, hydroxy, hydroxyalkyl, halo, nitro, oxo (=O), amino, N-protected amino, alkoxy, thioalkoxy and haloalkyl, jj) alkylsulfinyl, kk) alkylsulfonyl, ll) arylsulfonyl, mm) arylsulfonyloxy, nn) -C(=NOR₄₉)C(O)OR₅₀ wherein R₄₉ is hydrogen or loweralkyl and R₅₀ is hydrogen or a carboxy-protecting group, oo) alkoxy-carbonylalkyl, pp) carboxyalkyl, qq) cyanoalkyl, rr) alkylaminoalkyl, ss) N-protected alkylaminoalkyl, tt) dialkylaminoalkyl, uu) dioxoalkyl, vv) loweralkyl-C(O)-, ww) loweralkyl-C(S)-, xx) aryl-C(O)-, yy) aryl-C(S)-, zz) loweralkyl-C(O)-O-, aaa) loweralkyl-S-C(S)- bbb) N-protected amino, ccc) aminoalkyl-C(O)-, ddd) N-protected aminoalkyl-C(O)- eee) aminoalkyl-C(S)-, fff) N-protected aminoalkyl-C(S)-, ggg) aminoalkyl, hhh) N-protected aminoalkyl, iii) formyl, jjj) cyano, kkk) nitro, lll) spiroalkyl, mmm) oxoalkyloxy, nnn) R₅₃-L₂₂-, wherein L₂₂ is alkenylene or alkynylene and R₅₃ is aryl or heterocyclic wherein the heterocyclic is unsubstituted or substituted with one, two or three substituents independently selected from the group consisting of loweralkyl, hydroxy, hydroxyalkyl, halo, nitro, oxo (=O), amino, N-protected amino, alkoxy, thioalkoxy and haloalkyl, ooo) aryl-NH-C(O)-, ppp) R₅₄-N=N- wherein R₅₄ is aryl or heterocyclic wherein the heterocyclic is unsubstituted or substituted with one, two or three substituents independently selected from the group consisting of loweralkyl, hydroxy, hydroxyalkyl, halo, nitro, oxo (=O), amino, N-protected amino, alkoxy, thioalkoxy and haloalkyl, qqq) =N-R₅₅ wherein R₅₅ is hydrogen, aryl, heterocyclic, -S(O)₂-aryl or -S(O)₂-heterocyclic wherein the heterocyclic is unsubstituted or substituted with one, two or three substituents independently selected from the group consisting of loweralkyl, hydroxy, hydroxyalkyl, halo, nitro, oxo (=O), amino, N-protected amino, alkoxy, thioalkoxy and haloalkyl, rrr) diarylalkyl-N=N-, sss) aryl-N(R₅₆)- or arylalkyl-N(R₅₆)- wherein R₅₆ is hydrogen or an N-protecting group, ttt) aryl-sulfonylalkyl, uuu) heterocyclicsulfonylalkyl wherein the heterocyclic is unsubstituted or substituted with one, two or three substituents independently selected from the group consisting of loweralkyl, hydroxy, hydroxyalkyl, halo, nitro, oxo (=O), amino, N-protected amino, alkoxy, thioalkoxy and haloalkyl, vvv) =C(CN)(C(O)NH₂), www) =C(CN)(C(O)O-loweralkyl), xxx) heterocyclic or heterocyclicalkyl wherein the heterocyclic is unsubstituted or substituted with one, two or three substituents independently selected from the group consisting of loweralkyl, hydroxy, hydroxyalkyl, halo, nitro, oxo (=O), amino, N-protected amino, alkoxy, thioalkoxy and haloalkyl, yyy) hydroxythioalkoxy, zzz) aryloxyalkyl, aaaa) aryloxyalkylthioalkoxy, bbbb) dialkoxyalkyl, cccc) dithioalkoxyalkyl, dddd) arylalkyl-NH-L₂₃- wherein L₂₃ is an alkylene group, eeee) heterocyclicalkyl-NH-L₂₄- wherein L₂₄ is an alkylene group, ffff) aryl-S(O)₂-NH-L₂₅- wherein L₂₅ is an alkylene group, gggg) heterocyclic-S(O)₂-NH-L₂₆- wherein L₂₆ is an alkylene group, hhhh) aryl-C(O)-NH-L₂₇- wherein L₂₇ is an alkylene group and iiiii) heterocyclic-C(O)-NH-L₂₈-

wherein L_{28} is an alkylene group, $jjjj) R_{yy}(CH_2)_n-X-Y-Z-(CH_2)_m$ wherein R_{yy} is
1265 cycloalkyl, aryl and loweralkyl, n and m are independently 0-2, Z is O or absent, Y is
absent, CH_2 , $CHOH$ or $C(O)$, with the proviso that when X is O, Z is absent and with the
proviso that when Z is O, X is absent and with the proviso that when Y is $CHOH$, X and Z
are absent.

The term "(heterocyclic)alkoxy" as used herein refers to an alkoxy group to which is
1270 attached a heterocycle. The (heterocyclic)alkoxy groups of this invention can be optionally
substituted.

The term "(heterocyclic)alkyl" as used herein refers to a heterocyclic group as
defined above appended to a loweralkyl radical as defined above. Examples of heterocyclic
alkyl include 2-pyridylmethyl, 4-pyridylmethyl, 4-quinolinylmethyl and the like. The
1275 (heterocyclic)alkyl groups of this invention can be optionally substituted.

The term "(heterocyclic)oxy" as used herein refers to a heterocycle connected to the
parent molecular group through an oxygen atom. The (heterocyclic)oxy groups of this
invention can be optionally substituted.

The term "(heterocyclic)oxyalkyl" as used herein refers to a loweralkyl group to which is
1280 attached a (heterocyclic)oxy group. The (heterocyclic)oxyalkyl groups of this invention can
be optionally substituted.

The term "(heterocyclic)alkoxyalkyl" as used herein refers to an alkoxyalkyl group
to which is attached a heterocycle. The (heterocyclic)alkoxyalkyl groups of this invention
can be optionally substituted.

1285 The term "heterocycliccarbonyloxyalkyl" as used herein refers to a loweralkyl radical
to which is appended $R_{72}-C(O)-O-$ wherein R_{72} is a heterocyclic group. The
heterocycliccarbonyloxyalkyl groups of this invention can be optionally substituted.

The term "hydroxy" as used herein refers to $-OH$.

The term "hydroxyalkyl" as used herein refers to a loweralkyl radical to which is
1290 appended an hydroxy group. The hydroxyalkyl groups of this invention can be optionally
substituted.

The term "hydroxyarylalkyl" as used herein refers to an arylalkyl group to which is
appended a hydroxy group. The hydroxyarylalkyl groups of this invention can be
optionally substituted.

1295 The term "hydroxythioalkoxy" as used herein refers to $R_{51}S-$ wherein R_{51} is a
hydroxyalkyl group. The hydroxythioalkoxy groups of this invention can be optionally
substituted.

The term "loweralkyl" as used herein refers to branched or straight chain alkyl
groups comprising one to ten carbon atoms, including methyl, ethyl, propyl, isopropyl, n -

1300 butyl, t-butyl, neopentyl and the like. The loweralkyl groups of this invention can be optionally substituted.

The term "N-protected alkylaminoalkyl" as used herein refers to an alkylaminoalkyl group wherein the nitrogen is N-protected. The N-protected alkylaminoalkyl groups of this invention can be optionally substituted.

1305 The term "nitro" as used herein refers to $-\text{NO}_2$.

The term "oxo" as used herein refers to $(=\text{O})$.

The term "oxoalkyloxy" as used herein refers to an alkoxy radical wherein the loweralkyl moiety is substituted with an oxo $(=\text{O})$ group. The oxoalkyloxy groups of this invention can be optionally substituted.

1310 The term "oxyamino(alkyl)carbonylalkyl" as used herein refers to a $-\text{O}-\text{NR}-\text{C}(\text{O})-\text{R}'$ group wherein R and R' are loweralkyl.

The term "oxyamino(arylalkyl)carbonylalkyl" as used herein refers to a $-\text{O}-\text{NR}^{\text{R}_3}-\text{C}(\text{O})-\text{R}$ group wherein R^{R_3} is arylalkyl and R is loweralkyl.

1315 The term "oxyaminocarbonylalkyl" as used herein refers to $-\text{O}-\text{NH}-\text{C}(\text{O})-\text{R}$ group wherein R is loweralkyl.

The term "spiroalkyl" as used herein refers to an alkylene diradical, both ends of which are bonded to the same carbon atom of the parent group to form a spirocyclic group. The spiroalkyl groups of this invention can be optionally substituted.

The term "sulfhydryl" as used herein refers to $-\text{SH}$.

1320 The term "sulfhydrylalkyl" as used herein refers to a loweralkyl group to which is attached a sulfhydryl group. The sulfhydrylalkyl groups of this invention can be optionally substituted.

The term "thioalkoxy" as used herein refers to $\text{R}_{52}\text{S}-$ wherein R_{52} is loweralkyl. Examples of thioalkoxy include, but are not limited to, methylthio, ethylthio and the like.

1325 The thioalkoxy groups of this invention can be optionally substituted.

The term "thioalkoxyalkyl" as used herein refers to a thioalkoxy group as previously defined appended to a loweralkyl group as previously defined. Examples of thioalkoxyalkyl include thiomethoxymethyl, 2-thiomethoxyethyl and the like. The thioalkoxyalkyl groups of this invention can be optionally substituted.

1330 The term "thiocycloalkoxy" as used herein refers to a cycloalkyl group attached to the parent molecular group through a sulfur atom. The thiocycloalkoxy groups of this invention can be optionally substituted.

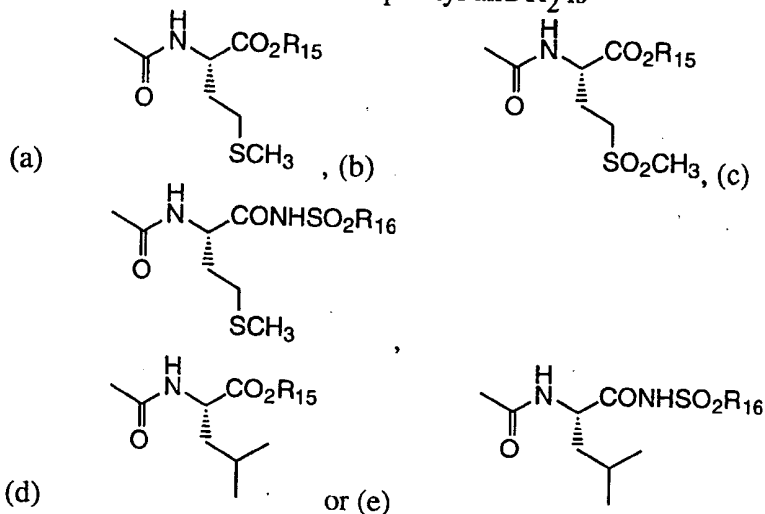
1335 The term "thiocycloalkoxyalkyl" as used herein refers to a loweralkyl group to which is attached a thiocycloalkoxy group. The thiocycloalkoxyalkyl groups of this invention can be optionally substituted.

Preferred embodiments

Preferred compounds of the invention are compounds of formula I wherein R_1 is unsubstituted or substituted phenyl and R_2 is $-C(O)NH-CH(R_{14})-C(O)OR_{15}$ or $-C(O)NH-CH(R_{14})-C(O)NHSO_2R_{16}$ wherein L_2 , R_{14} , R_{15} and R_{16} are defined above.

1340

More preferred compounds of the invention are compounds of formula I wherein R_1 is unsubstituted or substituted phenyl and R_2 is

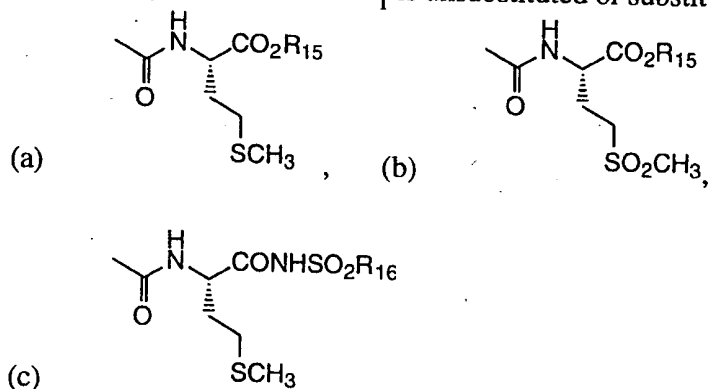


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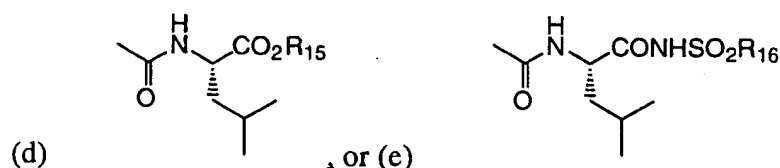
Still more preferred compounds have formula I wherein R_3 is selected from the group consisting of (a) pyridyl, (b) imidazolyl, and (c) furyl wherein the pyridyl, imidazolyl, or furyl group may be substituted with 1, 2 or 3 substituents selected from the group consisting of aryl, loweralkyl, halo, nitro, haloalkyl, hydroxy, hydroxyalkyl, amino, N-protected amino, alkoxy, and thioalkoxy.

1350

Still more preferred compounds of the invention have the structure defined immediately above wherein R_1 is unsubstituted or substituted phenyl and R_2 is



1355



1360 The most preferred compounds have the structure defined immediately above wherein R_3 is unsubstituted or substituted pyridyl or imidazolyl.

Protein Farnesyltransferase Inhibition

1365 The ability of the compounds of the invention to inhibit protein farnesyltransferase or protein geranylgeranyltransferase can be measured according to the method of Moores, et al., J. Biol. Chem. 266: 14603 (1991) or the method of Vogt, et al., J. Biol. Chem. 270:660-664 (1995). In addition, procedures for determination of the inhibition of farnesylation of the oncogene protein Ras are described by Goldstein, et al., J. Biol. Chem., 266:15575-15578 (1991) and by Singh in United States Patent No. 5,245,061.

1370 In addition, *in vitro* inhibition of protein farnesyltransferase may be measured by the following procedure. Rat brain protein farnesyltransferase activity is measured using an Amersham Life Science commercial scintillation proximity assay kit and substituting a biotin-K Ras B fragment (biotin-Lys-Lys-Ser-Lys-Thr-Lys-Cys-Val-Ile-Met- CO_2H), 0.1 mM final concentration, for the biotin-lamin substrate provided by Amersham. The enzyme is purified according to Reiss, Y., et al., Cell, 62: 81-88 (1990), utilizing steps one through three. The specific activity of the enzyme is approximately 10 nmol substrate farnesylated/mg enzyme/hour. The percent inhibition of the farnesylation caused by the compounds of the invention (at $10 \times 10^{-6} \text{ M}$) compared to an uninhibited control sample is evaluated in the same Amersham test system.

1380 The % inhibition of protein farnesyltransferase was determined for representative compounds of the invention. The results are summarized in Table 1.

Tables 1-5

In Vitro Potencies of Representative Compounds

1385 Table 1. Inhibition of farnesyltransferase

Example	% inhibition at 1×10^{-5} M	Example	% inhibition at 1×10^{-5} M
200	93	674	40
350	53	676	76
351	82	678	73
352	52	680	58
353	62	683	57
354	47	684	48
355	43	685	55
356	58	686	48
357	56	687	78
358	45	688	71
359	36	689	73
360	88	690	61
361	97	692	74
362	83	699	74
363	96	700	68
364	69	701	64
365	97	702	79
366	83	704	67
367	81	705	72
368	71	706	53
369	87	707	66
370	86	708	76
371	66	709	55
372	69	710	45
373	76	711	46
374	61	712	69
375	68	713	40
376	80	714	56
377	71	715	67
378	54	717	75

380	45	718	40
381	79	750	44
382	> 50	752	58
383	> 50	753	55
387	> 50	754	40
388	> 50	755	44
390	> 50	756	47
639	44	757	58
659	55	758	46
663	43	759	49
664	75	952	> 50
669	52	955	50
670	78	974	> 50
672	48		

Table 2. Inhibition of farnesyltransferase

Example	% inhibition at 1×10^{-6} M	Example	% inhibition at 1×10^{-6} M
157	92	583	98
158	2	587	97
159	84	595	97
160	30	607	96
161	54	610	94
162	12	613	97
163	18	617	99
164	92	620	98
165	74	626	61
166	97	627	85
167	98	632	43
168	92	633	32
183	98	636	72
184	36	641	34
185	93	642	48
186	86	644	54
187	68	386	> 50
188	40	399	> 50
189	88	403	99
190	4	404	98
191	28	405	98
192	95	406	95
193	4	407	98
196	43	435	96
197	1	451	85
201	63	452	96
202	31	453	90
203	76	456	81
204	98	457	92
205	98	460	88
206	67	463	91
207	98	465	92
208	98	466	93

209	74	467	97
210	5	468	96
211	98	469	92
212	12	470	95
213	98	471	94
214	97	472	97
215	82	473	96
216	67	474	92
217	99	475	21
218	89	476	91
219	56	477	98
220	92	478	98
221	55	479	95
222	41	480	87
223	63	481	95
224	41	488	41
225	93	494	96
226	23	495	95
227	94	496	93
228	39	497	94
231	50	498	98
233	65	499	98
234	4	500	98
235	95	501	84
237	98	502	24
238	22	503	57
239	97	504	90
240	98	505	72
241	41	507	95
242	99	507	96
243	23	508	95
244	21	509	77
245	50	510	84
248	79	512	94
249	77	513	96
250	96	514	94

252	98	515	72
253	99	516	95
254	96	525	99
255	98	528	99
256	98	529	99
257	98	530	94
258	98	537	97
259	98	540	40
260	98	645	37
261	98	646	58
262	98	649	86
263	99	650	68
264	98	651	33
265	98	652	41
266	97	653	62
267	96	655	35
268	98	657	32
269	98	658	73
270	98	661	45
271	84	662	68
272	96	665	55
273	96	666	82
274	94	667	83
276	98	671	36
277	98	673	59
278	99	677	37
279	99	682	31
280	98	691	34
281	98	693	53
282	76	694	45
283	98	696	57
284	83	697	39
286	84	703	40
287	24	716	69
288	22	719	90
289	23	720	70

290	74	721	83
291	23	722	96
292	36	723	87
294	98	724	87
295	94	725	78
296	89	726	81
297	65	727	95
298	43	744	84
299	94	749	84
300	22	751	32
301	98	764	88
302	31	765	76
304	99	768	67
305	99	771	72
306	99	772	79
307	82	773	41
308	62	774	48
309	98	775	32
310	98	776	36
311	97	777	83
313	94	782	96
314	97	786	34
315	93	787	70
316	63	788	44
317	54	789	86
318	98	790	88
319	98	791	53
320	93	792	88
321	90	793	94
322	98	794	92
323	98	796	35
324	98	797	35
325	99	806	72
326	91	807	90
327	97	808	88
328	96	809	78

329	98	810	89
330	98	812	94
331	98	813	95
332	26	816	87
333	99	824	90
334	93	831	92
343	72	832	80
344	95	834	55
345	91	835	96
346	98	844	92
347	95	846	85
348	66	850	90
349	99	862	95
379	21	866	62
541	37	867	71
542	67	868	89
544	35	872	74
545	88	878	95
546	97	879	95
547	91	886	35
550	96	889	95
	78	902	85
728			
552	88	903	78
553	92	908	88
554	96	910	42
555	85	911	65
556	99	918	97
557	93	923	78
560	91	924	77
561	91	925	87
564	98	926	69
565	94	936	
			69
566	98	937	95
568	93	962	> 50

569	91	964	> 50
572	91	979	26
575	70	982	64
576	88	987	93
577	94	988	92
582	99	989	88

1390

Table 3. Inhibition of farnesyltransferase

Example	% inhibition at 1×10^{-7} M	Example	% inhibition at 1×10^{-7} M
434	93	623	96
436	89	729	73
437	89	730	96
438	90	731	65
439	80	732	84
440	92	733	60
441	91	734	49
442	88	735	96
443	97	736	96
444	95	737	95
445	94	738	54
446	91	739	83
447	91	740	94
448	92	741	89
449	91	742	87
450	96	743	51
455	83	745	93
458	87	746	84
459	92	747	68
461	93	748	56
462	91	769	90
464	86	770	91
482	96	781	91
483	95	785	96
484	97	795	87
485	96	798	95
486	97	799	96
487	81	800	74
489	86	801	87
490	70	802	88
491	94	811	85
492	95	814	81
493	51	815	71

511	82	817	60
519	89	818	78
520	97	822	93
521	94	823	75
522	93	825	79
523	97	839	63
524	99	849	66
526	96	854	78
527	97	855	92
531	74	856	97
532	88	857	92
533	91	859	86
534	84	861	65
535	89	863	72
536	79	864	84
539	89	865	95
548	86	869	92
549	98	874	90
551	93	875	92
558	87	876	92
559	96	891	94
562	95	893	87
563	95	894	89
570	92	895	92
571	88	896	96
573	72	900	95
574	81	906	88
578	90	912	85
579	92	913	89
580	90	914	91
581	96	917	78
584	96	919	91
585	96	921	82
589	91	929	81
590	95	931	98
592	93	933	91

593	86	935	72
594	95	940	92
597	75	941	90
600	93	945	80
601	92	947	79
602	97	948	75
604	86	949	57
609	95	950	71
611	95	951	71
615	94	959	> 50
616	95	983	66
618	89	984	86
621	98	990	84
622	95	993	90

Table 4. Inhibition of farnesyltransferase

Example	% inhibition at 1×10^{-8} M	Example	% inhibition at 1×10^{-8} M
384	91	851	82
397	50	852	79
398	> 50	853	85
400	98	858	60
401	66	860	85
408	> 95	870	91
409	84	871	94
410	94	873	97
517	92	877	68
518	90	880	95
567	69	881	69
586	90	882	79
588	68	883	91
591	82	884	94
599	86	885	95
603	94	887	92
605	68	888	86
606	93	892	59
608	91	897	76
612	96	898	82
614	92	899	88
619	95	901	84
760	95	904	85
762	84	905	86
763	92	907	79
766	95	909	79
767	97	916	96
779	70	920	96
780	71	922	96
803	95	927	74
804	95	928	84
805	96	930	66
819	76	932	60

820	66	934	71
821	75	938	61
826	92	939	72
827	77	942	58
828	87	943	79
829	92	944	88
833	78	946	52
836	95	954	> 50
837	91	958	> 50
838	92	960	> 50
840	73	985	89
841	93	986	95
842	88	991	69
843	96	992	93
845	85	994	83
847	85	995	92
848	87	996	80

Table 5. Inhibition of geranylgeranyltransferase I.

Example	Activity
387	> 50% inhibition at 1×10^{-6} M
388	> 50% inhibition at 1×10^{-7} M
389	> 50% inhibition at 1×10^{-6} M
390	> 50% inhibition at 1×10^{-5} M
392	> 50% inhibition at 1×10^{-5} M
399	> 50% inhibition at 1×10^{-6} M
953	> 50% inhibition at 1×10^{-6} M
955	> 50% inhibition at 1×10^{-7} M
962	> 50% inhibition at 1×10^{-7} M
964	> 50% inhibition at 1×10^{-6} M
966	> 50% inhibition at 1×10^{-6} M
967	> 50% inhibition at 1×10^{-6} M
969	> 50% inhibition at 1×10^{-5} M
974	> 50% inhibition at 1×10^{-5} M

1395

Table 6. Inhibition of farnesyltransferase at concentrations of 10 mM and 1 mM unless specified as * (0.1 mM) or ** (0.01 mM)

Example	% inhibition 10 mM	% inhibition 1 mM	Example	% inhibition 10 mM	% inhibition 1 mM
997		91**	1199		71
998		79**	1200		97*
999		90	1201		73*
1000		82*	1202		96**
1001		92**	1203		84*
1002		82**	1204		93*
1003		92*	1205		55**
1004		92**	1206		63**
1005		95**	1207		91*
1006		95**	1208		89*
1007		85**	1209		87*
1008		95**	1210		64**
1009		86**	1211		94
1010		90*	1212		86*

1011		92**	1213		79**
1012		88*	1214		92**
1013		80*	1215		17
1014		91	1216		88**
1015		59*	1217		87*
1016		92*	1218		54**
1017		51*	1219		85**
1018		97	1220		
1019		70	1221		82**
1020		39	1222		89*
1021		93*	1223		91**
1022		91**	1224		88*
1023		89**	1225		92**
1024		89**	1226		69**
1025		91**	1227		91
1026		74**	1228		88*
1027		81**	1229		66**
1028		92**	1230		77**
1029		82**	1231		93*
1030		92**	1232		68**
1031		90**	1233		77**
1032		93**	1234		71**
1033		76**	1235		86**
1034		77	1236		83**
1035		76	1237		89**
1036		79	1238		91**
1037		88	1239		85*
1038		57	1240		64**
1039		89**	1241		74*
1040		90**	1242		75*
1041		48	1243		95*
1042		88	1244		84
1043		90*	1245		92
1044		76*	1246		82

1045		86*	1247		95*
1046		93	1248		88
1047		95	1249		89
1048		78**	1250		79**
1049		93**	1251		91**
1050		62**	1252		84*
1051		79**	1253		76*
1052		91**	1254		67
1053		60**	1255		82*
1054		89**	1256		95*
1055		85**	1257		93**
1056		75**	1258		97**
1057		82*	1259		89**
1058		89	1260		90**
1059		92*	1261		94
1060		42	1262		95
1061		88*	1263		85*
1062		93	1264		83**
1063		92**	1265		90
1064		95**	1266		85*
1065		78*	1267		96
1066		73**	1268		95*
1067		93*	1269		84**
1068		79**	1270		91**
1069		74*	1271		78**
1070		93**	1272		73**
1071		95*	1273		94*
1072		82*	1274		89*
1073		93**	1275		86**
1074		82	1276		88**
1075		90**	1277		90**
1076		69**	1278		68
1077		93**	1279		87**
1078		86*	1280		78**

1079		90	1281		81*
1080		87	1282		69*
1081		61	1283		74*
1082		84*	1284		86
1083		88	1285		94
1084		76**	1286		85**
1085		93*	1287		95**
1086		87*	1288		69*
1087		76*	1289		93
1088		73*	1290		80
1089		86*	1291		
1090		81**	1292		
1091		87*	1293		
1092		74**	1294		
1093		95**	1295		
1094		96**	1296		
1095		76*	1297		
1096		86*	1298		97**
1097		80**	1299		96**
1098		60*	1300		97*
1099		87**	1301		97*
1100		82**	1302		93**
1101		86*	1303		91**
1102		84**	1304		90**
1103		92*	1305		91**
1104		89**	1306		85**
1105		91**	1307		85**
1106		67**	1308		91**
1107		88**	1309		96*
1108		95**	1310		90**
1109		74**	1311		95**
1110			1312		91**
1111		63**	1313		91**
1112		62	1314		96*

1113		55	1315		86*
1114		83**	1316		78*
1115		94*	1317	99	96
1116		91**	1318		
1117		92*	1319		79**
1118		86*	1320		79
1119		84**	1321		
1120		93	1322		
1121		72*	1323		
1122		92**	1324		
1123		90*	1325		
1124		90*	1326		
1125		92*	1327		
1126		87	1328		
1127		90*	1329		
1128		86*	1330		
1129		92**	1331		
1130		88**	1332		92**
1131		96**	1333		95*
1132		97*	1334		72**
1133		75*	1335		90*
1134		95**	1336		74
1135		88*	1337		83**
1136		91	1338		65*
1137		83**	1339		
1138		65*	1340		77*
1139		92*	1341		89
1140		77**	1342		
1141		80*	1343		88
1142		84**	1344		93**
1143		92*	1345		94**
1144		76*	1346		94*
1145		83*	1347		81**
1146		61**	1348		78**

1147		93*	1349		92**
1148		79**	1350		
1149		94*	1351		
1150		92*	1352		
1151		91*	1353		
1152		96*	1354		38
1153		89*	1355		46
1154		93*	1356		80
1155		91*	1357		78
1156		87	1358		
1157		66**	1359		
1158	75		1360		98**
1159		72*	1361		96*
1160		83*	1362		83**
1161		87*	1363		88**
1162		84*	1364		
1163		73**	1365		
1164		94	1366		79*
1165		84*	1367		93*
1166		74**	1368		92**
1167		91*	1369		94*
1168		88*	1370		86**
1169		77	1371		94*
1170		74*	1372		95**
1171		74**	1373		95**
1172		38*	1374		93**
1173		89**	1375		80**
1174		79**	1376		86**
1175		96	1377		95*
1176		97*	1378		68
1177		19	1379		41
1178		88**	1380		87**
1179		85*	1381		65**
1180		93*	1382		86**

1181		82*	1383		88*
1182		92**	1384		69**
1183		79**	1385		93*
1184		84**	1386		88*
1185		85**	1387		82**
1186		93**	1392		93*
1187		93**	1397		87**
1188		93**	1398		81*
1189		74**	1399		94
1190		95**	1400		95
1191		85**			
1192		91*			
1193		95**			
1194		78**			
1195		94*			
1196		87*			
1197		85*			
1198		86*			

* % inhibition at 0.1 μ M

** % inhibition at 0.01 μ M

1400

Additional methods for the measurement of *in vitro* inhibition of protein prenylation (i.e., inhibition of farnesyltransferase or geranylgeranyltransferase) are described below.

Assays are performed using the glass fiber filter binding assay procedure with either rabbit reticulocyte lysate or FTase or GGTase I fractions isolated from bovine brains using a combination of hydrophobic and DEAE column chromatography procedures. Protein substrates are purchased from Panvera Corporation (H-ras for FTase, H-ras-CVLL for GGTase I). Tritium labeled prenyl lipid substrates (FPP or GGPP) are obtained from Amersham Life Science.

1410

FTase

³H-Farnesyl diphosphate (final concentration 0.6 μ M), H-Ras (final concentration 5.0 μ M) and the test compound (various final concentrations from a stock solution in 50% DMSO/water; final concentration DMSO < 2%) were mixed in buffer (50 mM HEPES (pH 7.5), 30 mM MgCl₂, 20 mM KCl, 10 μ M ZnCl₂, 5 mM DTT, 0.01% Triton X-100) to give

1415 a final volume of 50 μ L. The mixture was brought to 37 °C, enzyme was added, and the
reaction is incubated for 30 minutes. 1 mL of 1 M HCl/ethanol was added to stop the
reaction, and the mixture was allowed to stand for 15 minutes at room temperature then
diluted with 2 mL of ethanol. The reaction mixture was filtered through a 2.5 cm glass
1420 microfiber filter from Whatman and washed with four 2 mL portions of ethanol. The glass
filter was transferred to a scintillation vial and 5 mL of scintillation fluid was added. The
radioisotope retained on the glass fiber filter was counted to reflect the activity of the
enzymes. The IC₅₀ value was calculated by measuring the activity of the enzyme over a
suitable range of inhibitor concentrations.

1425

GGTase I

³H-geranylgeranyldiphosphate (final concentration 0.5 μ M), H-Ras-CVLL (final
concentration 5.0 μ M) and the test compound (various final concentrations from a stock
solution in 1:1 DMSO/water; final concentration DMSO < 2%) were mixed in buffer (50
mM Tris-HCl (pH 7.2), 30 mM MgCl₂, 20 mM KCl, 10 μ M ZnCl₂, 5 mM DTT, 0.01%
1430 Triton X-100) to give a final volume of 50 μ L. The mixture was brought to 37 °C, treated
with enzyme, and incubated for 30 minutes. 1 mL of 1 M HCl/ethanol was added to stop the
reaction, and the mixture was allowed to stand for 15 minutes at room temperature then
diluted with 2 mL of ethanol. The reaction mixture was filtered through a 2.5 cm glass
microfiber filter from Whatman and washed with four 2 mL portions of ethanol. The glass
1435 filter was transferred to a scintillation vial, and 5 mL scintillation fluid was added. The
radioisotope retained on the glass fiber filter was counted to reflect the activity of the
enzymes. The IC₅₀ value was calculated by measuring the activity of the enzyme over a
suitable range of inhibitor concentrations.

1440 Additionally, the ability of the compounds of the invention to inhibit prenylation in
whole cells, inhibit anchorage-independent tumor cell growth and inhibit human tumor
xenograft in mice could be demonstrated according to the methods described in PCT Patent
Application No. WO95/25086, published September 21, 1995, which is hereby
incorporated herein by reference.

1445

Pharmaceutical Compositions

The compounds of the present invention can be used in the form of pharmaceutically
acceptable salts derived from inorganic or organic acids. These salts include, but are not
limited to, the following: acetate, adipate, alginate, citrate, aspartate, benzoate,
benzenesulfonate, bisulfate, butyrate, camphorate, camphorsulfonate, digluconate,
1450 cyclopentanepropionate, dodecylsulfate, ethanesulfonate, glucoheptanoate,

glycerophosphate, hemisulfate, heptanoate, hexanoate, fumarate, hydrochloride, hydrobromide, hydroiodide, 2-hydroxy-ethanesulfonate, lactate, maleate, methanesulfonate, nicotinate, 2-naphthalenesulfonate, oxalate, pamoate, pectinate, persulfate, 3-phenylpropionate, picrate, pivalate, propionate, succinate, tartrate, thiocyanate, p-toluenesulfonate and undecanoate. Also, the basic nitrogen-containing groups can be quaternized with such agents as loweralkyl halides (such as methyl, ethyl, propyl, and butyl chloride, bromides, and iodides), dialkyl sulfates like dimethyl, diethyl, dibutyl, and diamyl sulfates, long chain halides such as decyl, lauryl, myristyl and stearyl chlorides, bromides and iodides, aralkyl halides like benzyl and phenethyl bromides, and others. Water or oil-soluble or dispersible products are thereby obtained.

Examples of acids which may be employed to form pharmaceutically acceptable acid addition salts include such inorganic acids as hydrochloric acid, sulphuric acid and phosphoric acid and such organic acids as oxalic acid, maleic acid, succinic acid and citric acid.

Basic addition salts can be prepared *in situ* during the final isolation and purification of the compounds of formula (I)-(XII) or separately by reacting the carboxylic acid function with a suitable base such as the hydroxide, carbonate or bicarbonate of a pharmaceutically acceptable metal cation or with ammonia or an organic primary, secondary or tertiary amine. Such pharmaceutically acceptable salts include, but are not limited to, cations based on the alkali and alkaline earth metals such as sodium, lithium, potassium, calcium, magnesium, aluminum salts and the like as well as nontoxic ammonium, quaternary ammonium, and amine cations including, but not limited to, ammonium, tetramethylammonium, tetraethylammonium, methylamine, dimethylamine, trimethylamine, triethylamine, ethylamine and the like. Other representative organic amines useful for the formation of base addition salts include diethylamine, ethylenediamine, ethanolamine, diethanolamine, piperazine and the like.

The compounds of the invention are useful (in humans and other mammals) for inhibiting protein isoprenyltransferases (i.e., protein farnesyltransferase and/or protein geranylgeranyltransferase) and the isoprenylation (i.e., farnesylation and/or geranylgeranylation) of Ras. These inhibitors of protein isoprenyltransferases are also useful for inhibiting or treating cancer in humans and other mammals. Examples of cancers which may be treated with the compounds of the invention include, but are not limited to, carcinomas such as lung, colorectal, bladder, breast, kidney, ovarian, liver, exocrine pancreatic, cervical, esophageal, stomach and small intestinal; sarcomas such as osteosarcoma, osteosarcoma, lipoma, liposarcoma, hemangioma and hemangiosarcoma; melanomas such as amelanotic and melanotic; mixed types of cancers such as carcinosarcoma, lymphoid tissue type, follicular reticulum, cell sarcoma and Hodgkins disease and leukemias, such as

myeloid, acute lymphoblastic, chronic lymphocytic, acute myeloblastic and chronic myelocytic.

1490 The ability of the compounds of the invention to inhibit or treat cancer can be demonstrated according to the methods of Mazerska Z., Woynarowska B., Stefanska B., Borowski S., *Drugs Exptl. Clin. Res.* 13(6), 345-351 (1987) Bissery, M.C., Guenard F., Guerritte-Voegelein F., Lavelle F., *Cancer Res.* 51, 4845-4852 (1991) and Rygaard J., and Povlsen C., *Acta Pathol. Microbiol. Scand.* 77, 758 (1969), which are hereby incorporated
1495 herein by reference.

These inhibitors of protein isoprenyltransferases are also useful for treating or preventing restenosis in humans and other mammals. The ability of the compounds of the invention to treat or prevent restenosis can be demonstrated according to the methods described by Kranzhofer, R. et al. *Circ. Res.* 73: 264-268 (1993), Mitsuka, M. et al. *Circ. Res.* 73: 269-275 (1993) and Santoian, E.C. et al. *Circulation* 88: 11-14 (1993),
1500 which are hereby incorporated herein by reference.

For use as a chemotherapeutic agent, the total daily dose administered to a host in single or divided doses may be in amounts, for example, from 0.01 to 500 mg/kg body weight daily, preferably in amounts from 0.1 to 20 mg/kg body weight daily and more
1505 preferably in amounts from 0.5 to 10 mg/kg body weight daily. Dosage unit compositions may contain such amounts of submultiples thereof to make up the daily dose.

For treatment or prevention of restenosis, the total daily dose administered to a host in single or divided doses may be in amounts, for example, from 0.001 to 1000 mg/kg body weight daily and more preferred from 1.0 to 50 mg/kg body weight daily. Dosage unit
1510 compositions may contain such amounts of submultiples thereof to make up the daily dose.

The amount of active ingredient that may be combined with the carrier materials to produce a single dosage form will vary depending upon the host treated and the particular mode of administration.

It will be understood, however, that the specific dose level for any particular patient
1515 will depend upon a variety of factors including the activity of the specific compound employed, the age, body weight, general health, sex, diet, time of administration, route of administration, rate of excretion, drug combination and the severity of the particular disease undergoing therapy.

The compounds of the present invention may be administered orally, parenterally, sublingually, by inhalation spray, rectally or topically in dosage unit formulations containing
1520 conventional nontoxic pharmaceutically acceptable carriers, adjuvants, and vehicles. Topical administration may also involve the use of transdermal administration such as transdermal patches or iontophoresis devices. The term parenteral as used herein includes

subcutaneous injections, intravenous, intramuscular, intrasternal injection or infusion techniques.

Injectable preparations, for example sterile injectable aqueous or oleagenous suspensions, may be formulated according to the known art using suitable dispersing or wetting and suspending agents. The sterile injectable preparation may also be a sterile injectable solution or suspension in a nontoxic parenterally acceptable diluent or solvent (as in a solution in 1,3-propanediol, for example). Among the acceptable vehicles and solvents that may be employed are water, Ringer's solution and isotonic sodium chloride solution. Additionally, sterile, fixed oils are conventionally employed as a solvent or suspending medium. For this purpose, any bland fixed oil may be employed including synthetic mono- or diglycerides. Fatty acids such as oleic acid find use in the preparation of injectables.

Suppositories for rectal administration of the drug can be prepared by mixing the drug with a suitable nonirritating excipient such as cocoa butter and polyethylene glycols which are solid at ordinary temperatures but liquid at rectal temperature and will therefore melt in the rectum and release the drug.

Solid dosage forms for oral administration may include capsules, tablets, pills, powders and granules. In such solid dosage forms, the active compound may be admixed with at least one inert diluent such as sucrose, lactose or starch. These dosage forms may also comprise additional substances other than inert diluents such as lubricating agents like magnesium stearate. With capsules, tablets and pills, the dosage forms may also comprise buffering agents. Tablets and pills may also be prepared with enteric coatings.

Liquid dosage forms for oral administration may include pharmaceutically acceptable emulsions, solutions, suspensions, syrups and elixirs containing inert diluents commonly used in the art such as water. Such compositions may also comprise adjuvants such as wetting agents, emulsifying and suspending agents and sweetening, flavoring, and perfuming agents.

The compounds of the present invention can also be administered in the form of liposomes. As is known in the art, liposomes are generally derived from phospholipids or other lipid substances. Liposomes are formed by mono- or multi-lamellar hydrated liquid crystals dispersed in an aqueous medium. Any non-toxic, physiologically acceptable and metabolizable lipid capable of forming liposomes can be used. The present compositions in liposome form can contain, in addition to a compound of the present invention, stabilizers, preservatives, excipients and the like. The preferred lipids are the phospholipids and phosphatidyl cholines (lecithins), both natural and synthetic.

Methods to form liposomes are known in the art. See, for example, Prescott, Ed., Methods in Cell Biology, Volume XIV, Academic Press, New York, N.Y. (1976), p. 33 *et seq.*, which is hereby incorporated herein by reference.

While the compounds of the invention can be administered as the sole active pharmaceutical agent for the treatment of cancer, they can also be used in combination with one or more other chemotherapeutic agents.

Representative examples of chemotherapeutic agents are described in Holleb, et al.,
1565 Clinical Oncology, American Cancer Society, United States (1991) p 56 *et seq.*, which is hereby incorporated herein by reference. These agents include alkylating agents such as the nitrogen mustards (mechloethamine, melphalan, chlorambucil, cyclophosphamide and ifosfamide), nitrosoureas (carmustine, lomustine, semustine, streptozocin), alkyl sulfonates (busulfan), triazines (dacarbazine) and ethylenimines (thiotepa, hexamethylmelamine); folic
1570 acid analogues (methotrexate); pyrimidine analogues (5-fluorouracil, cytosine arabinoside); purine analogues (6-mercaptopurine, 6-thioguanine); antitumor antibiotics (actinomycin D, the anthracyclines (doxorubicin), bleomycin, mitomycin C, methramycin); plant alkaloids such as vinca alkaloids (vincristine and vinblastine) and etoposide (VP-16); hormones and hormone antagonists (tamoxifen and corticosteroids); and miscellaneous agents (cisplatin,
1575 taxol and brequinar).

The above compounds to be employed in combination with the isoprenyl protein transferase inhibitor of the invention will be used in therapeutic amounts as indicated in the Physicians' Desk Reference (PDR) 47th Edition (1993), which is incorporated herein by reference or by such therapeutically useful amounts as would be known to one of ordinary
1580 skill in the art.

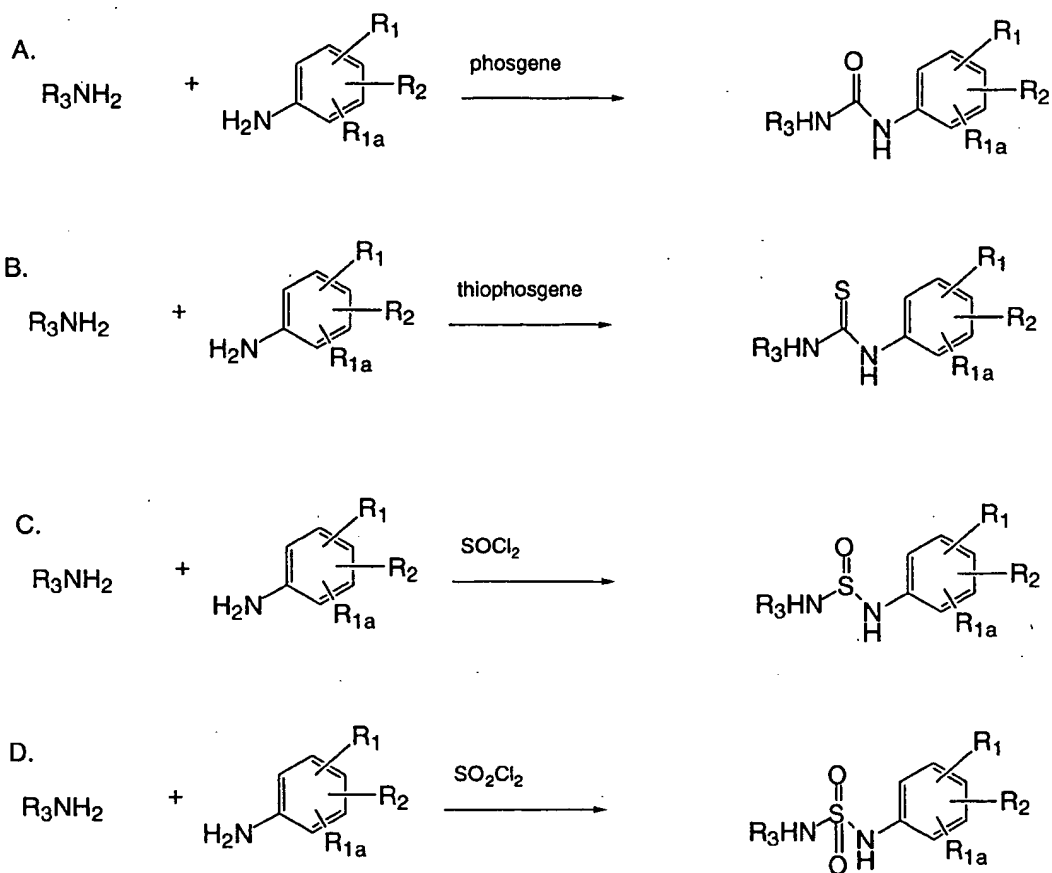
The compounds of the invention and the other chemotherapeutic agent can be administered at the recommended maximum clinical dosage or at lower doses. Dosage levels of the active compounds in the compositions of the invention may be varied to obtain a desired therapeutic response depending on the route of administration, severity of the
1585 disease and the response of the patient.

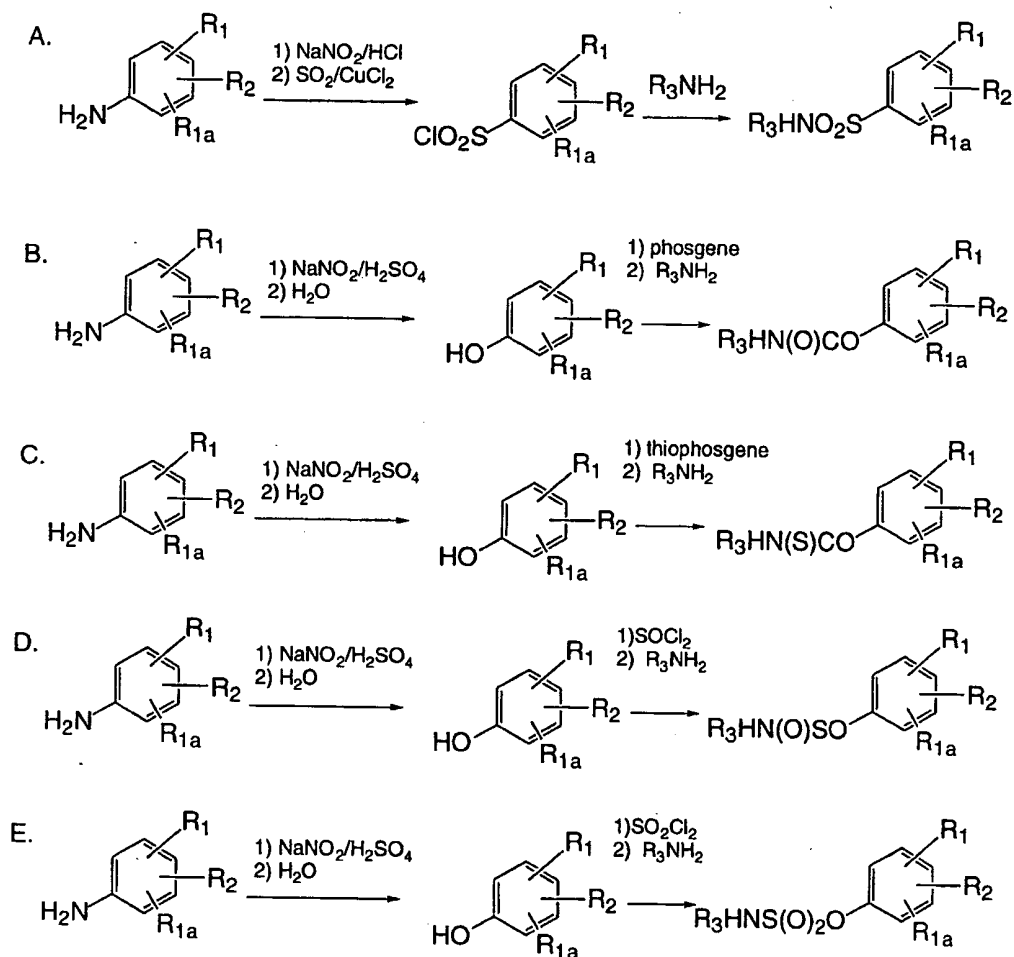
When administered as a combination, the therapeutic agents can be formulated as separate compositions which are given at the same time or different times, or the therapeutic agents can be given as a single composition.

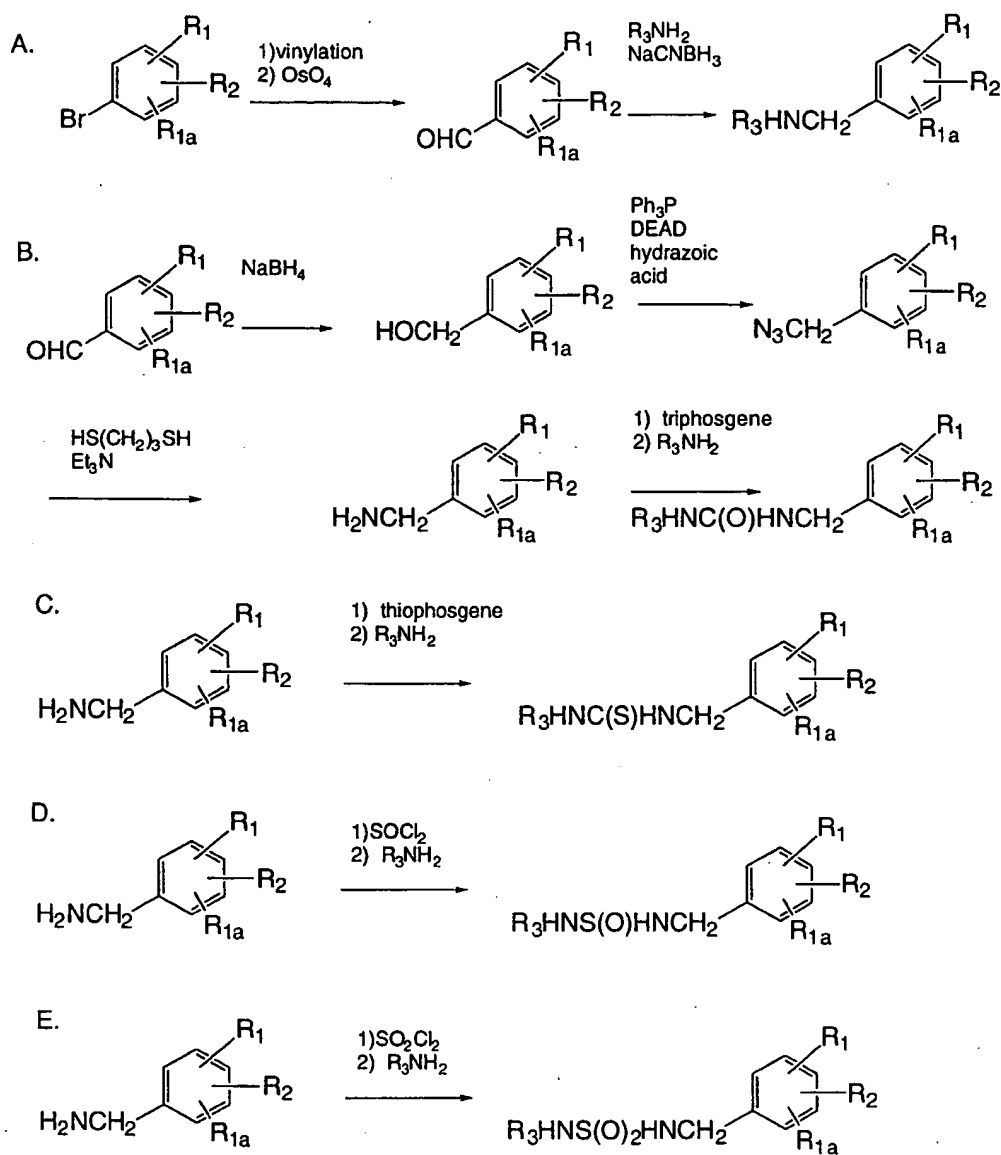
1590 Preparation of the Compounds of the Invention

In general, the compounds of the invention can be prepared by the processes illustrated in the following Schemes 1-16. In these general schemes compounds of the formula I are used to exemplify the methods, but the methods are intended to be applicable to all of the compounds of the invention.

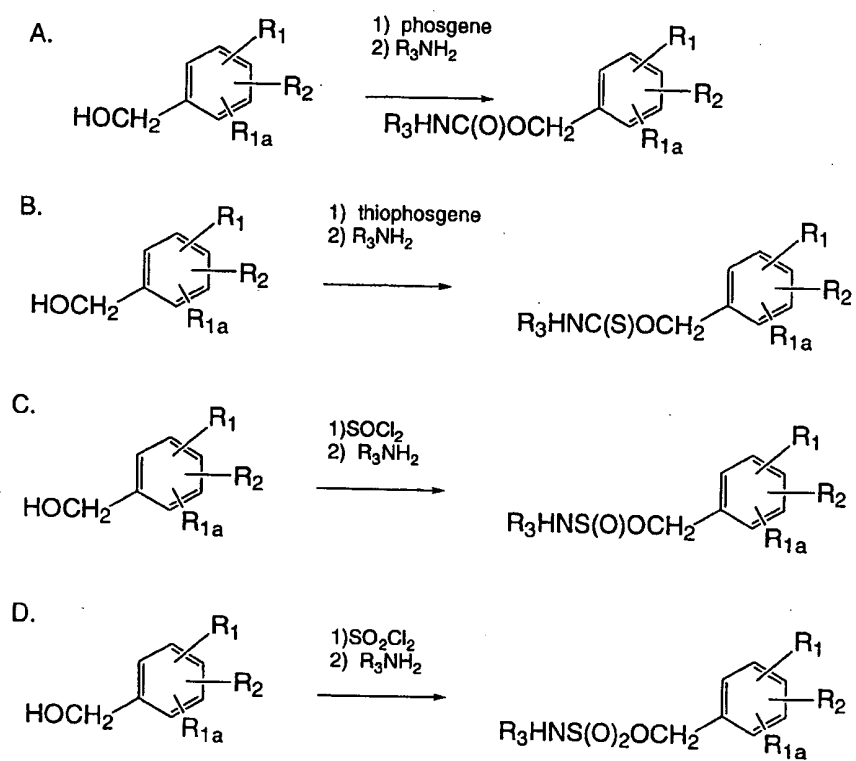
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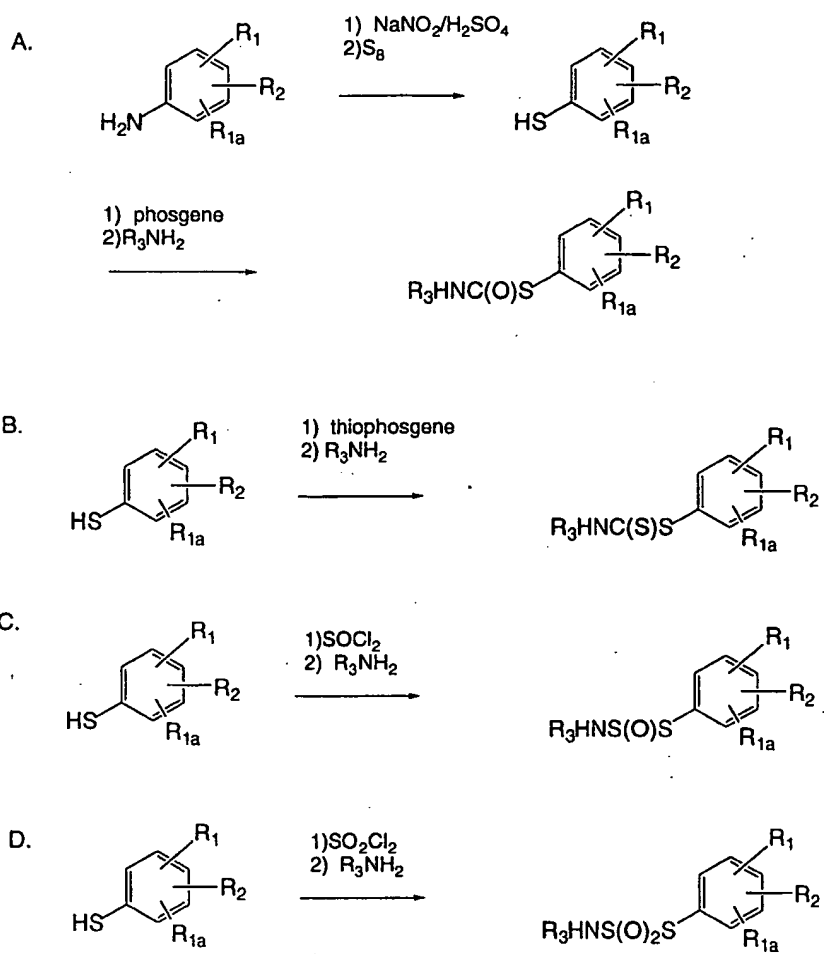
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SCHEME 2

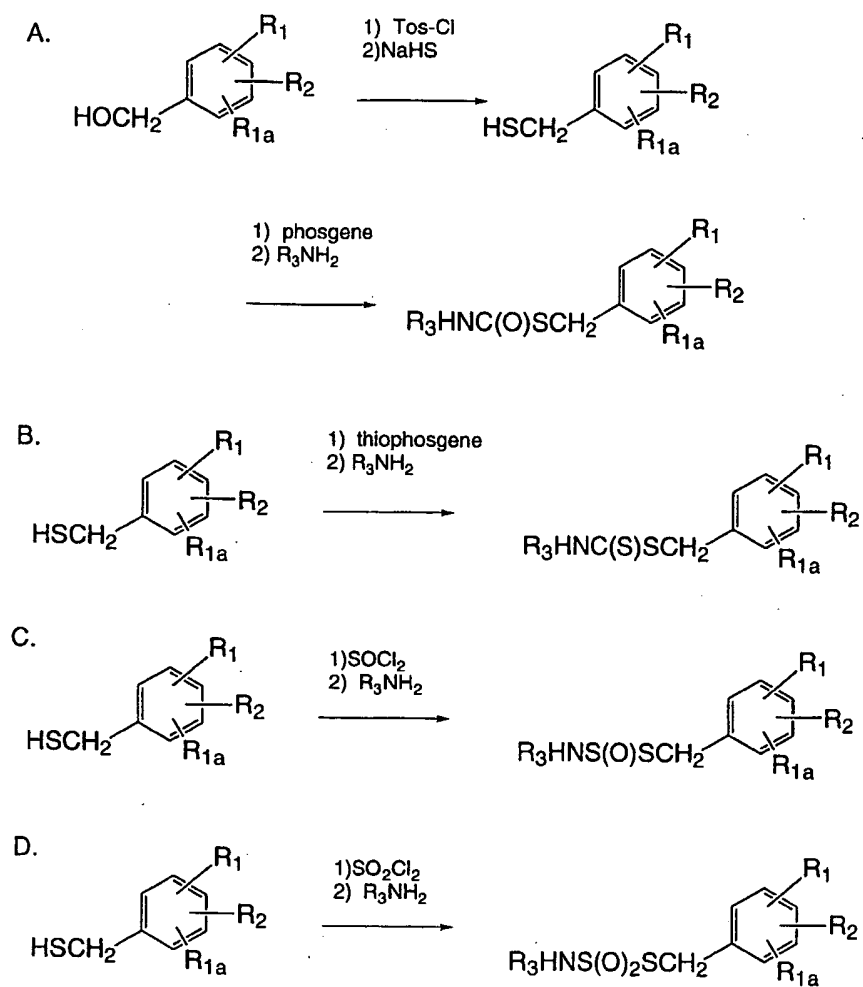
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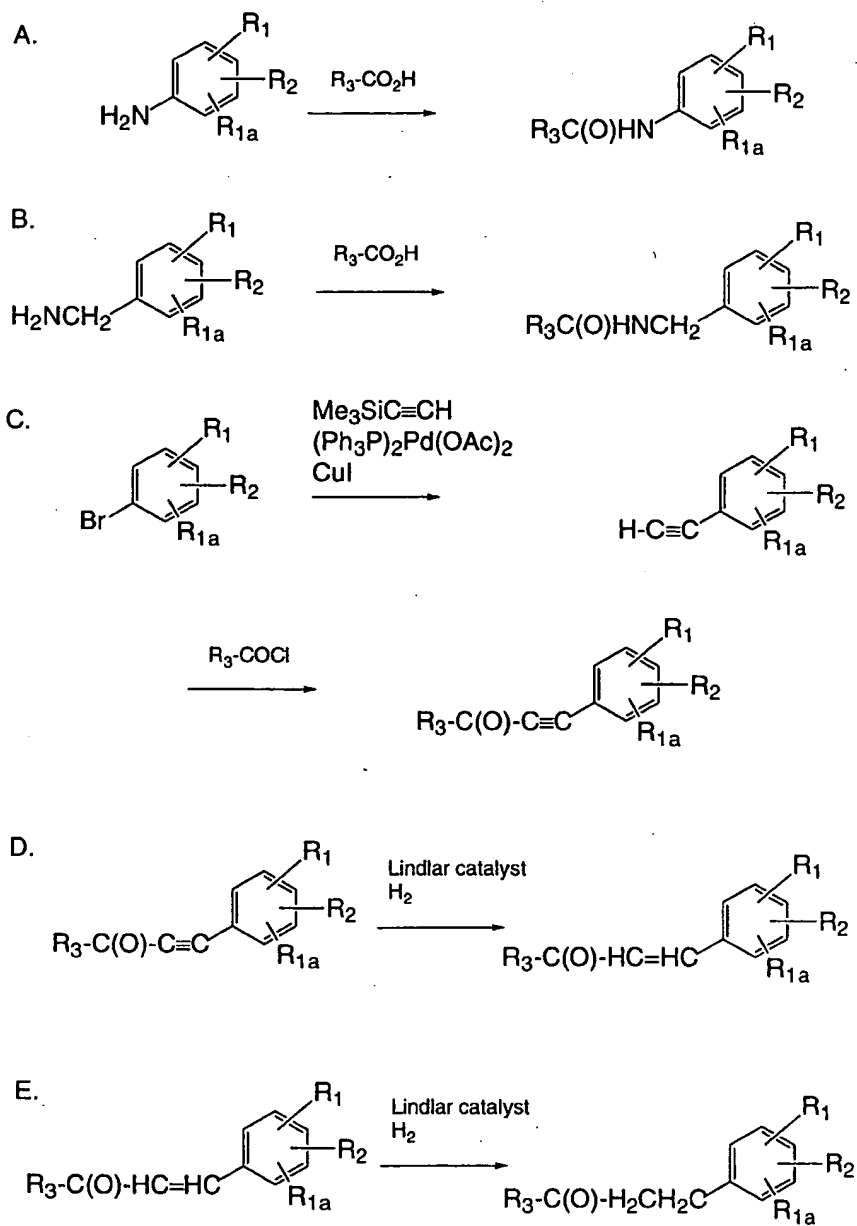
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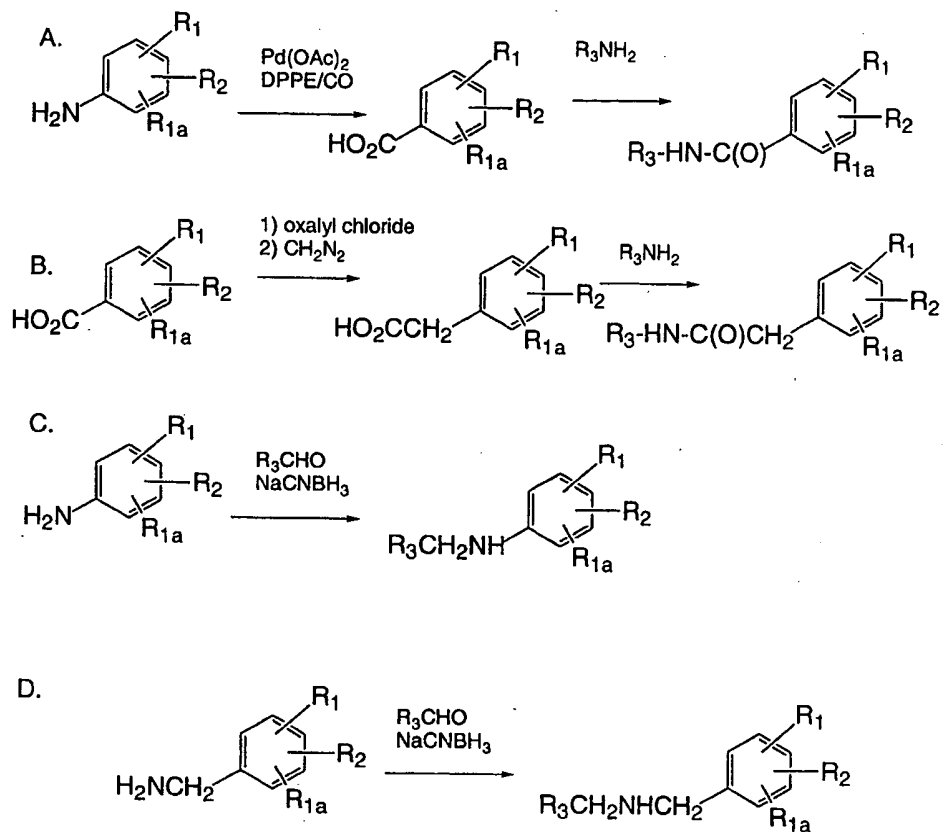
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SCHEME 5

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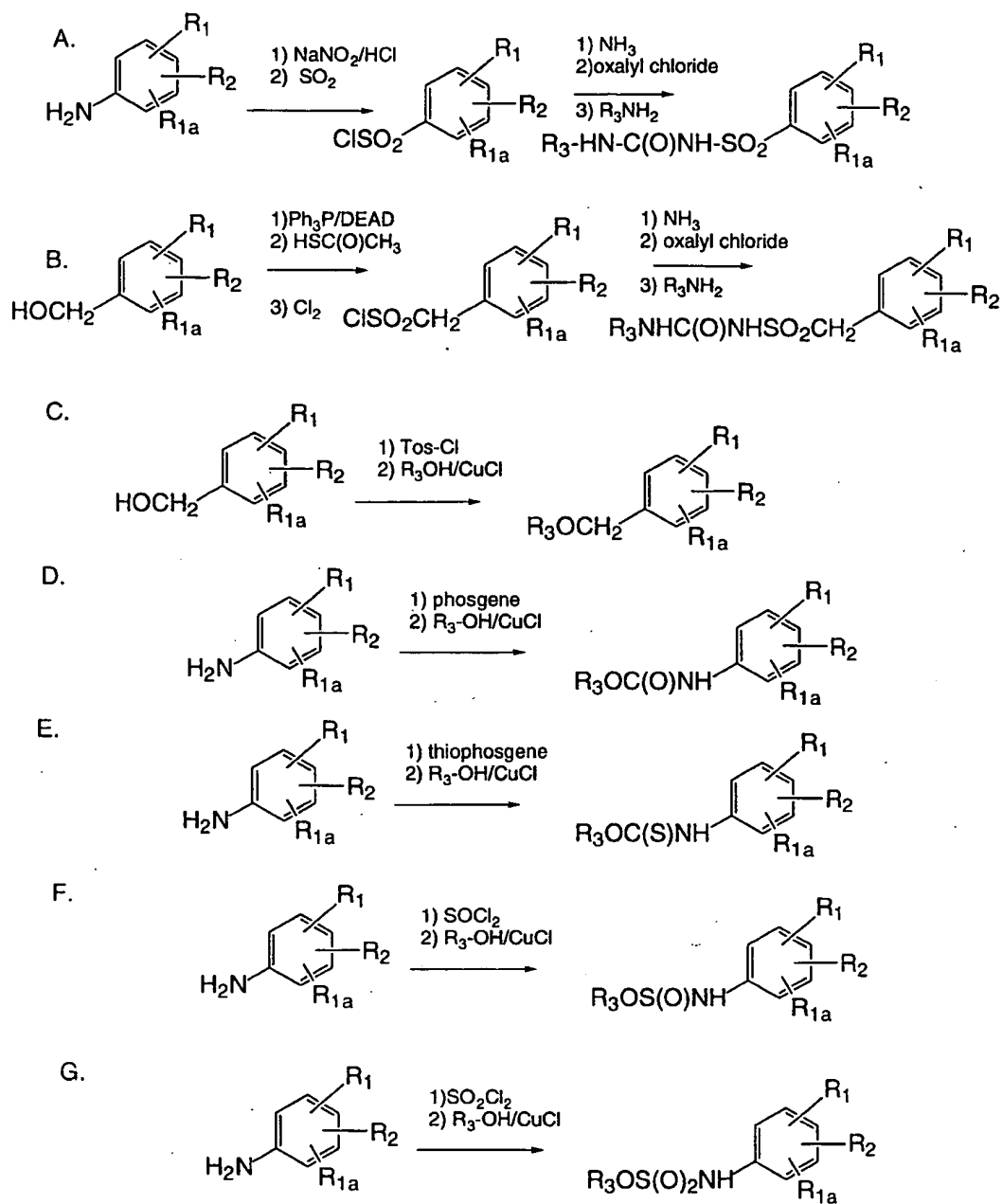
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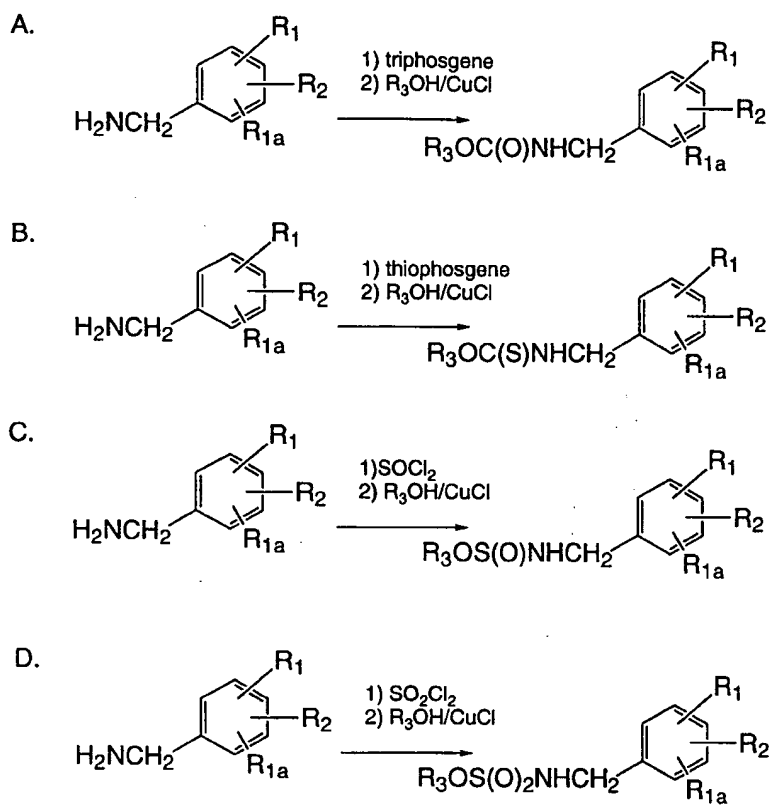
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SCHEME 8

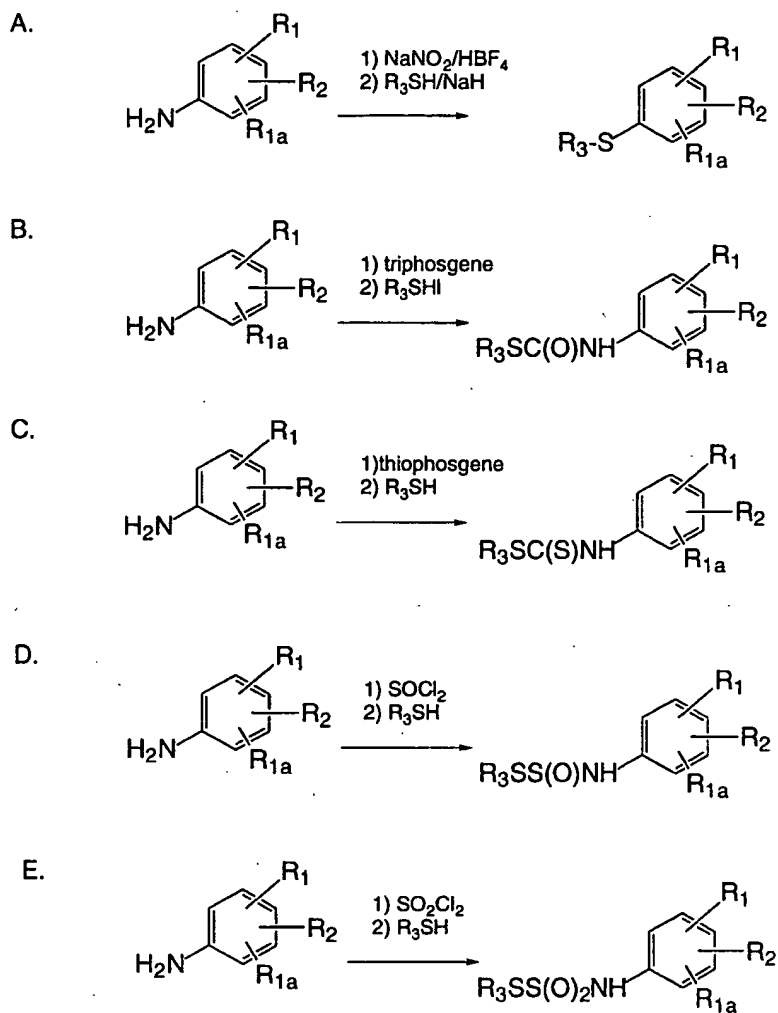
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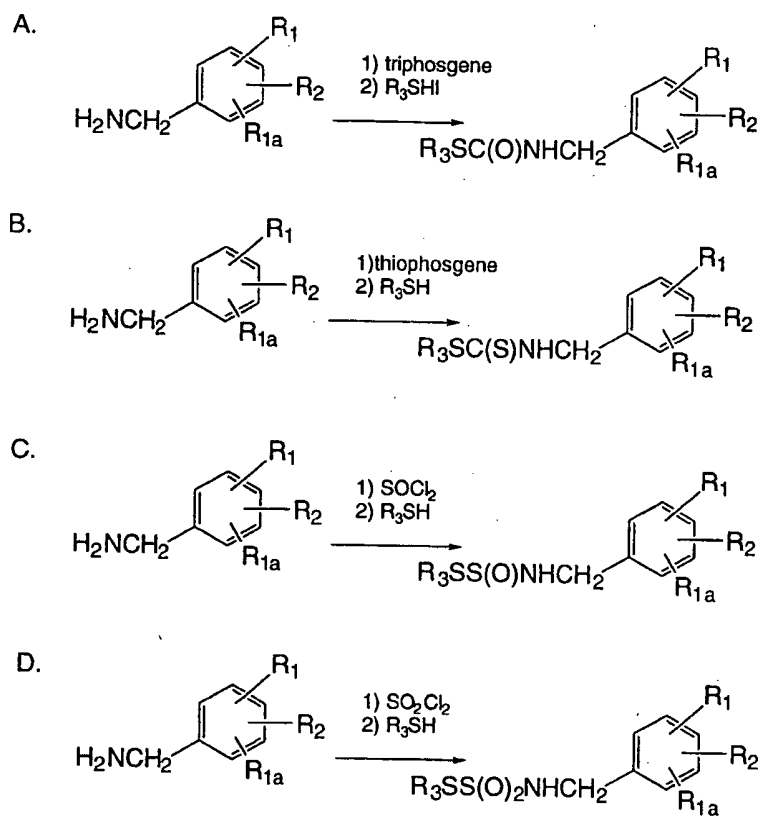
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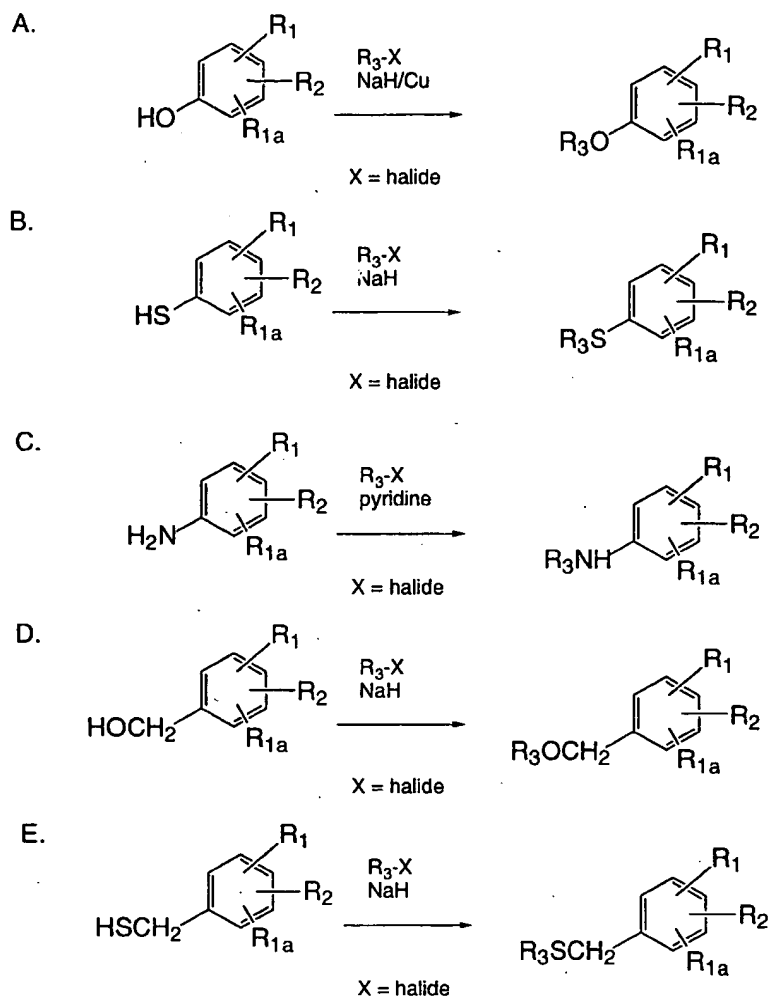


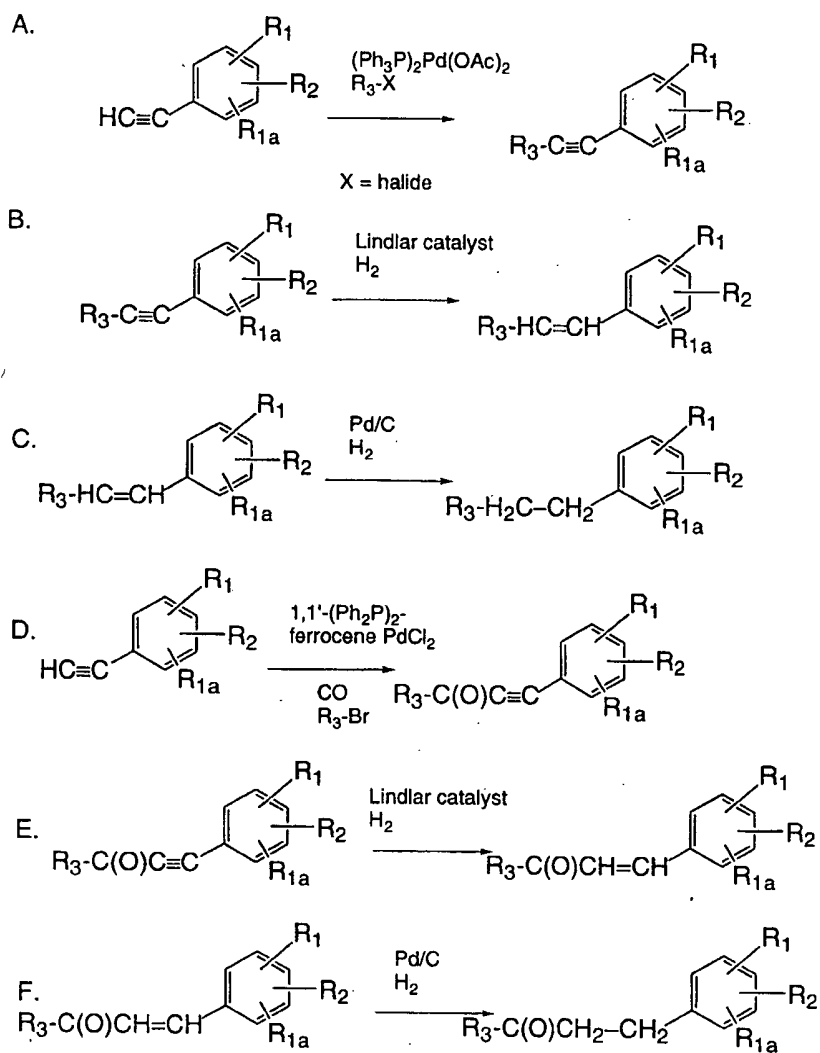
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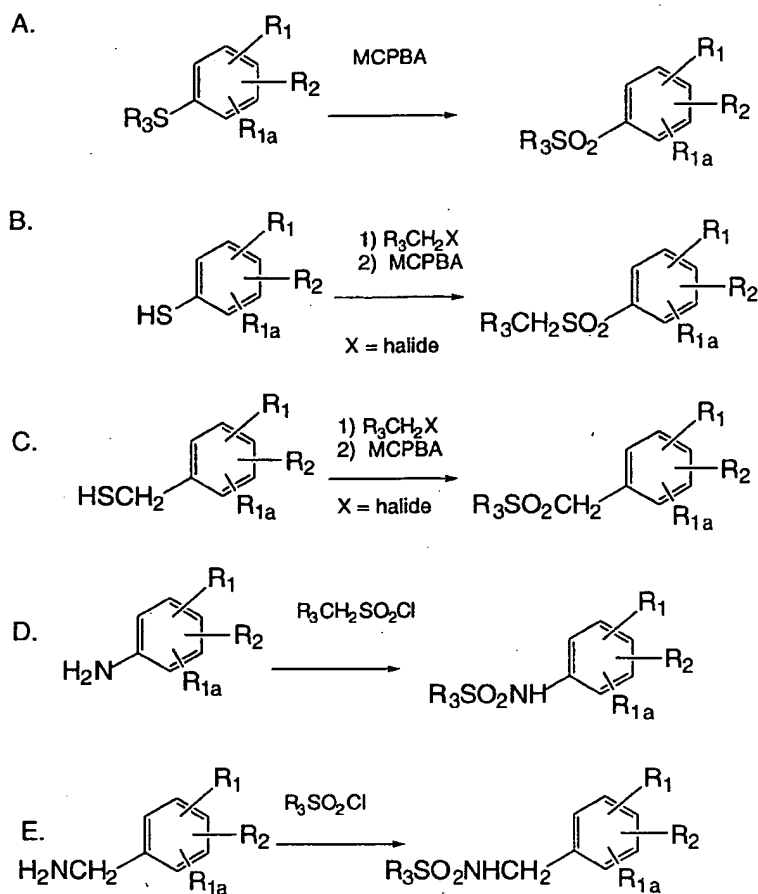
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SCHEME 11

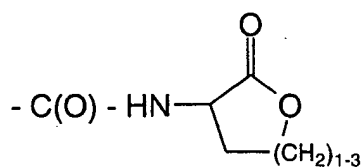
SCHEME 12

SCHEME 13

SCHEME 14

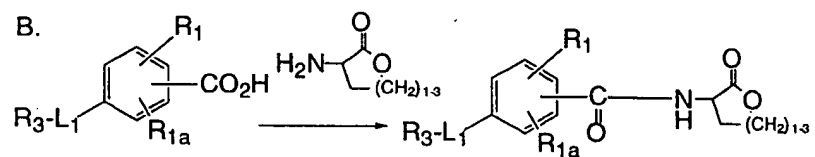
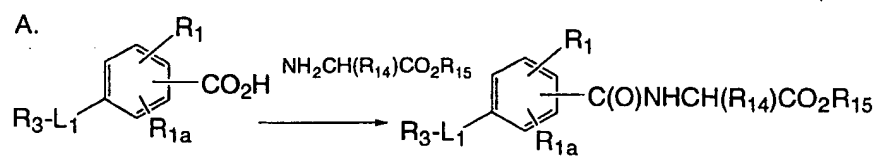
SCHEME 15

Scheme 16 illustrates an alternative method for preparing compounds wherein R_2 is $-C(O)NH-CH(R_{14})-C(O)OR_{15}$ or

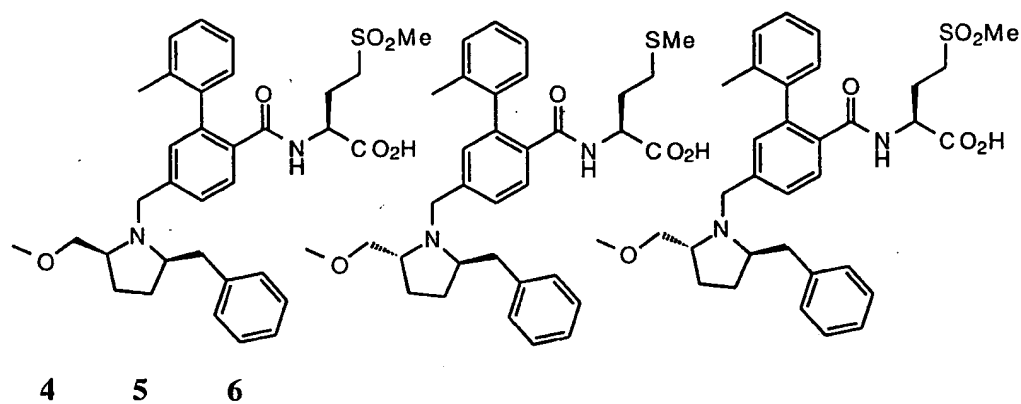
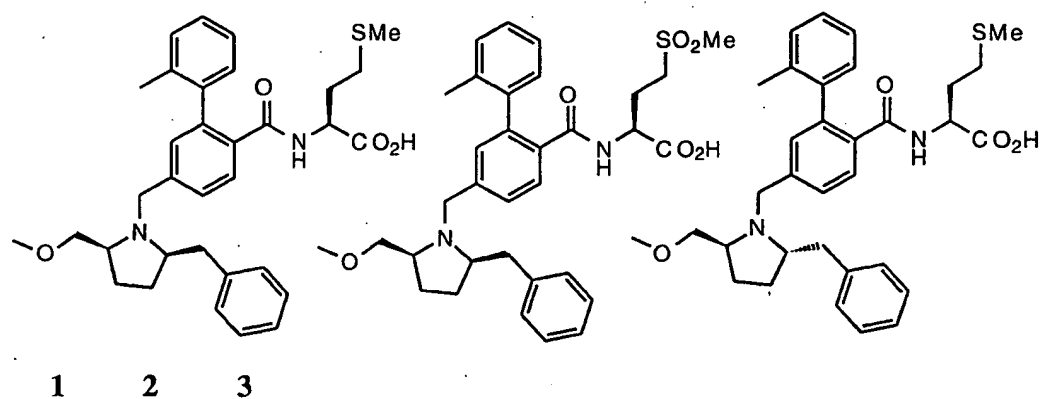


as defined above.

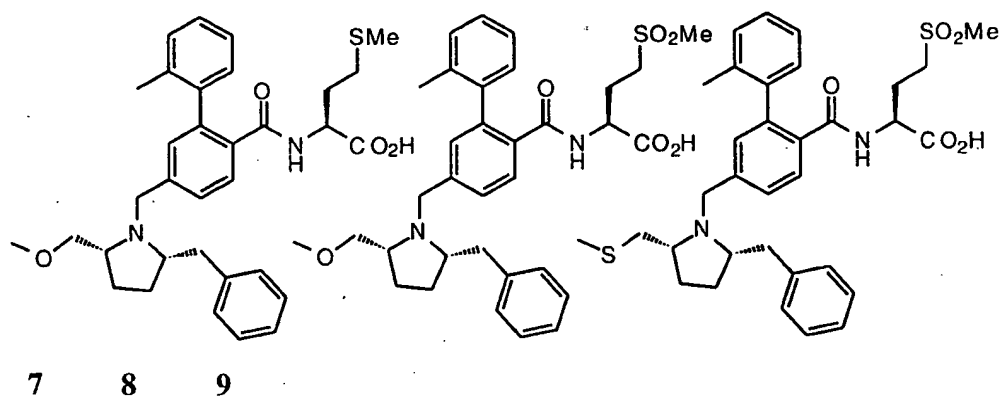
SCHEME 16



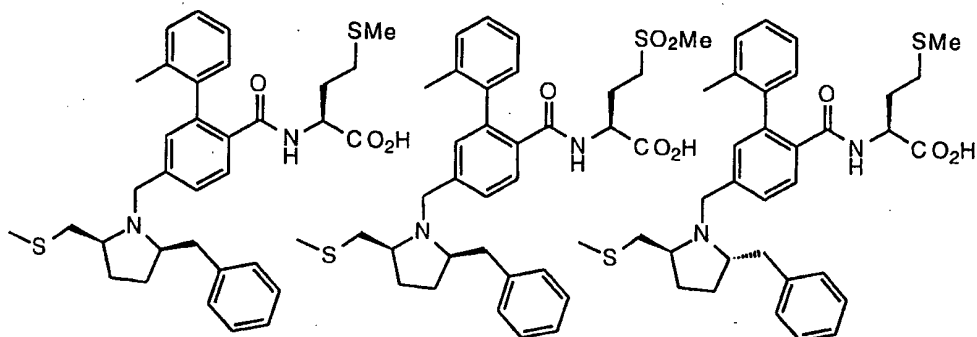
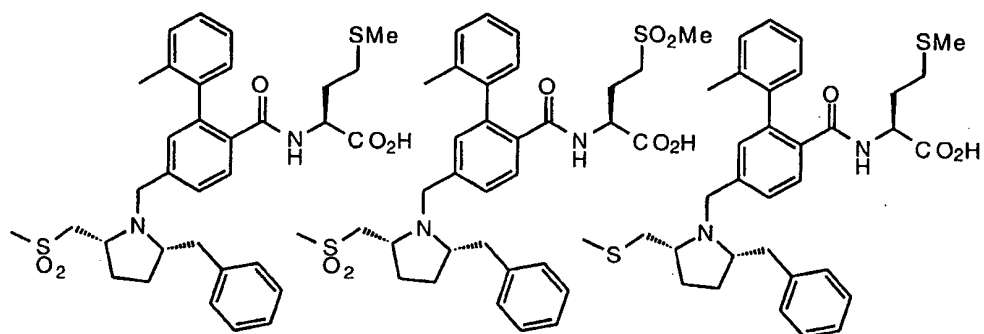
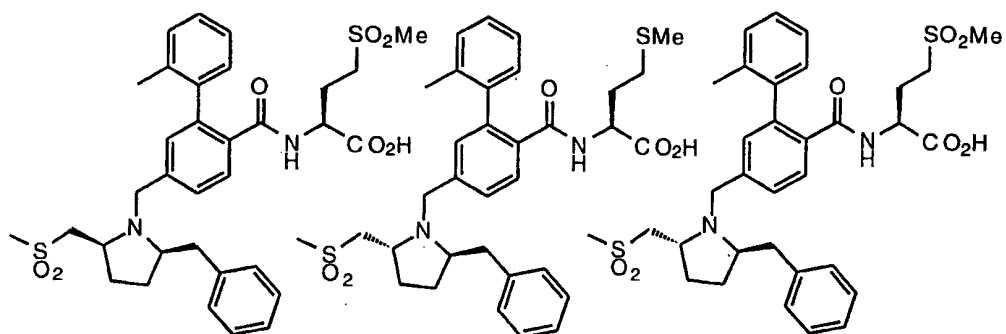
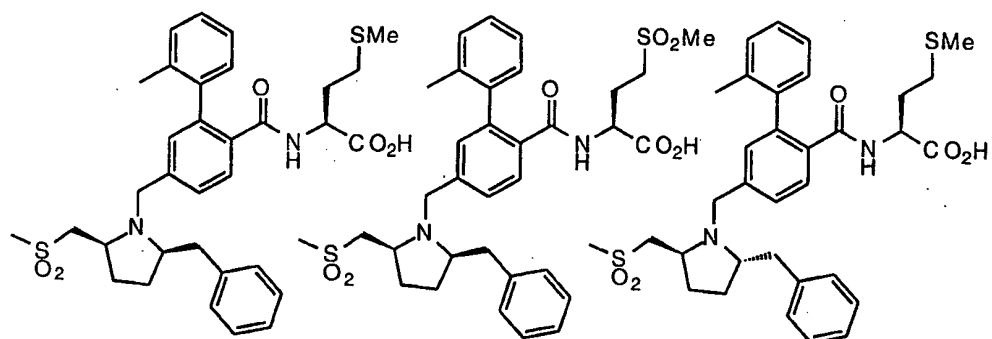
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Table 6. Amines of the Type A(B)N-L₁

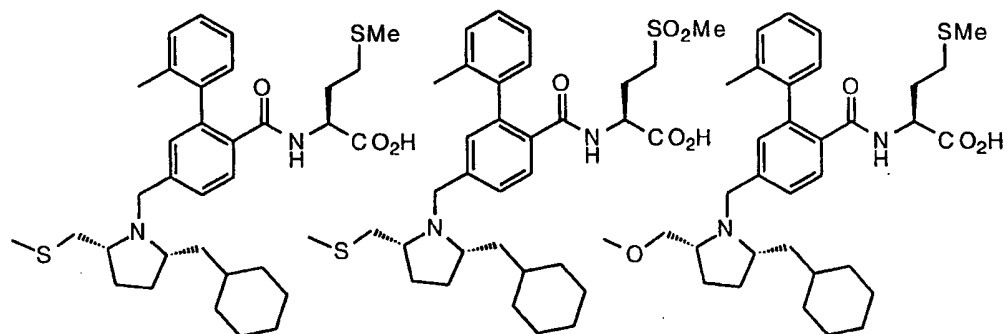
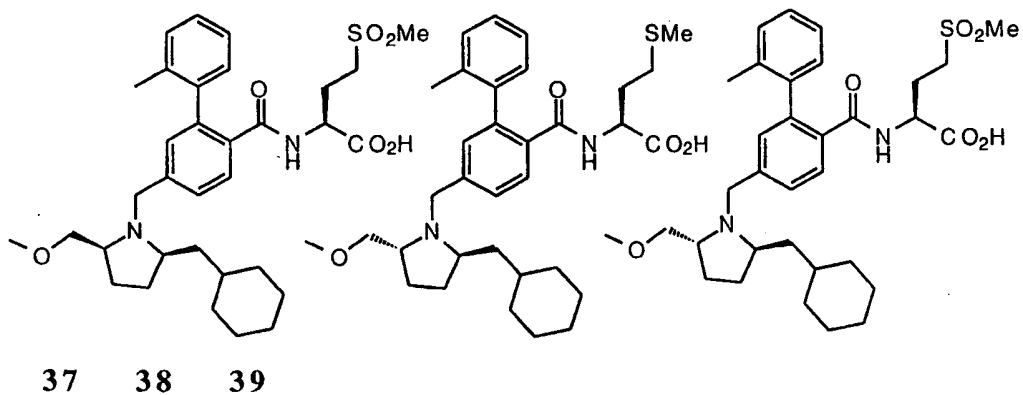
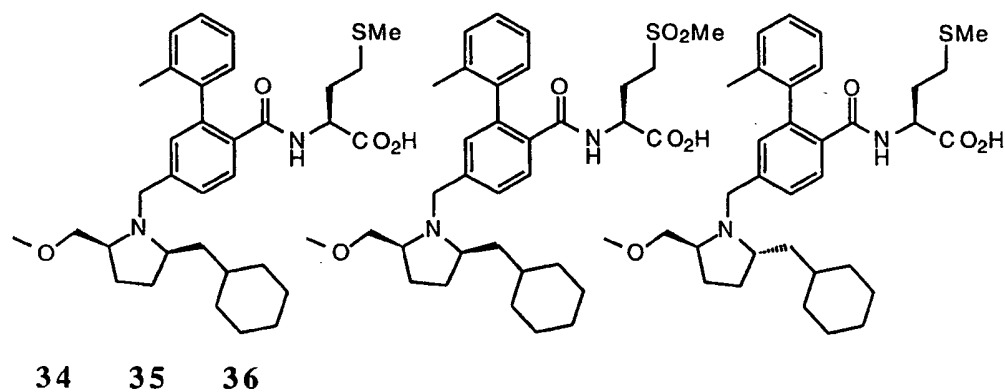
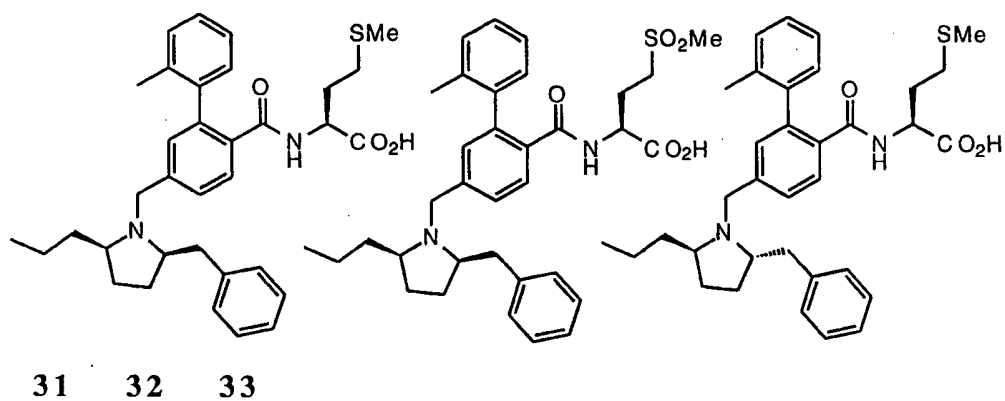
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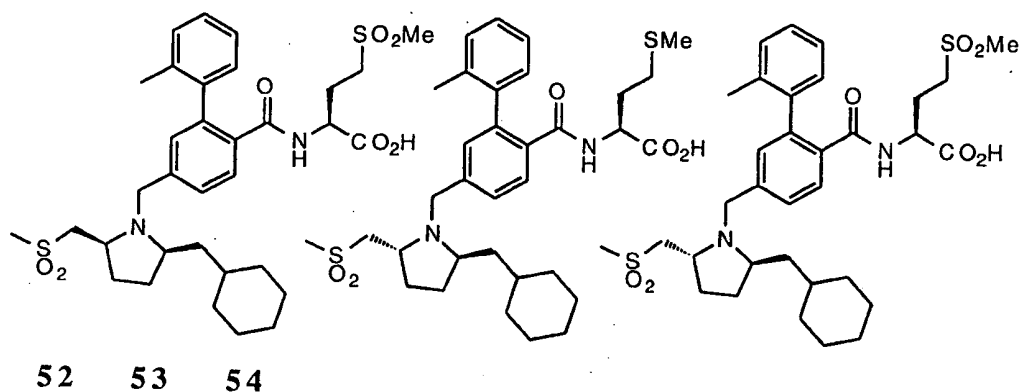


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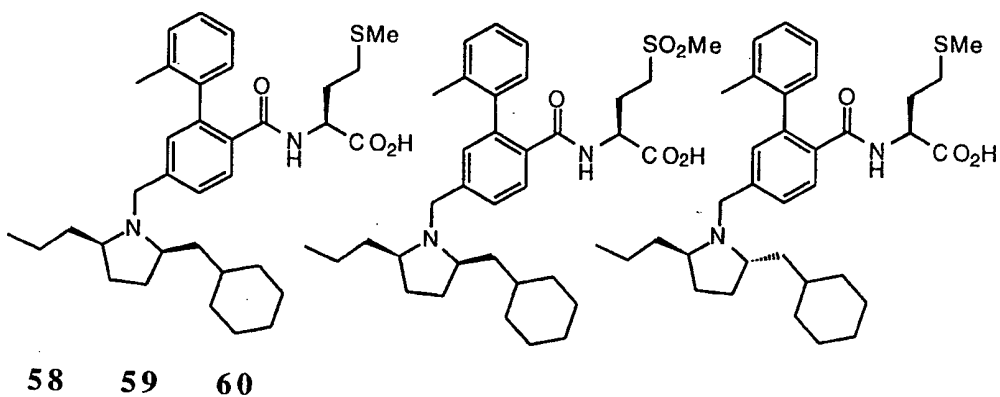
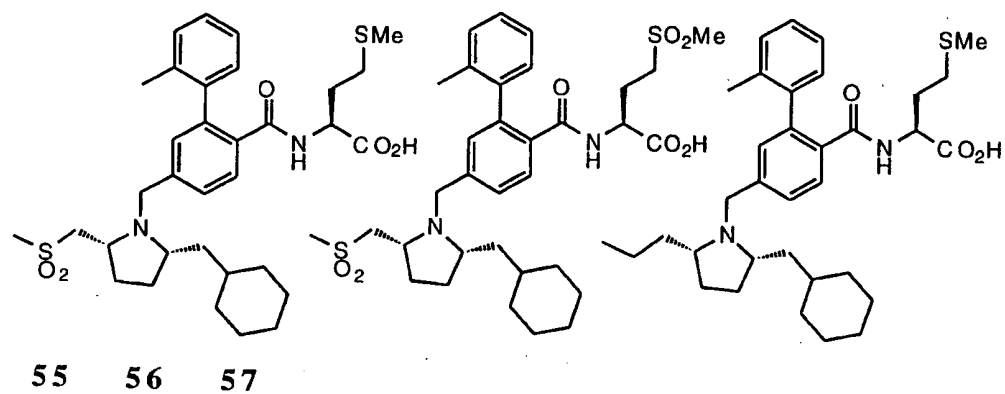


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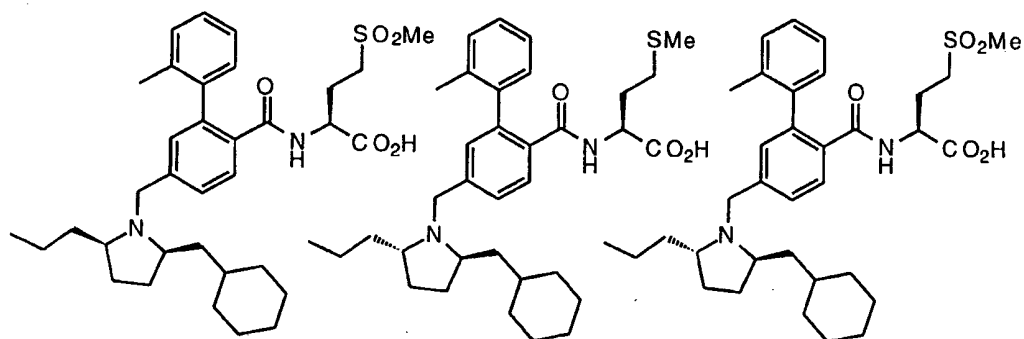
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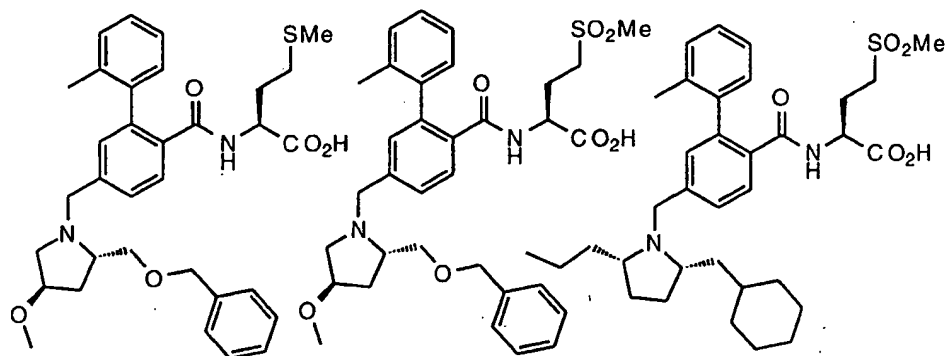
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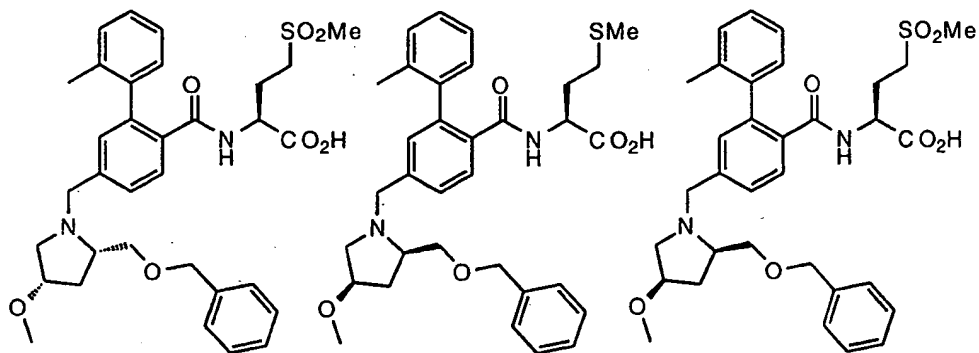


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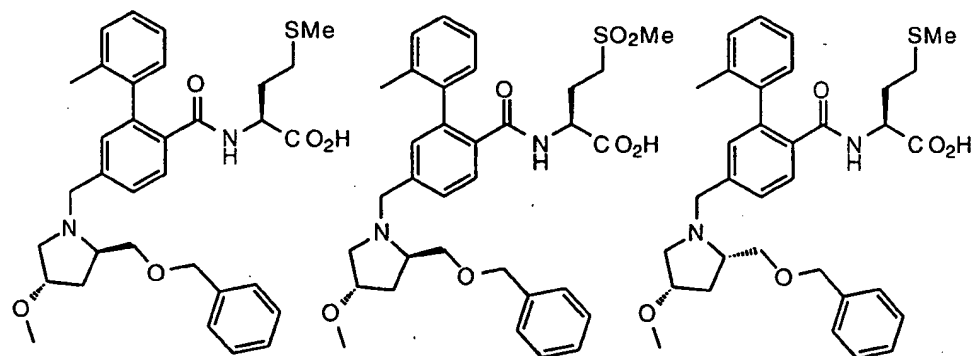


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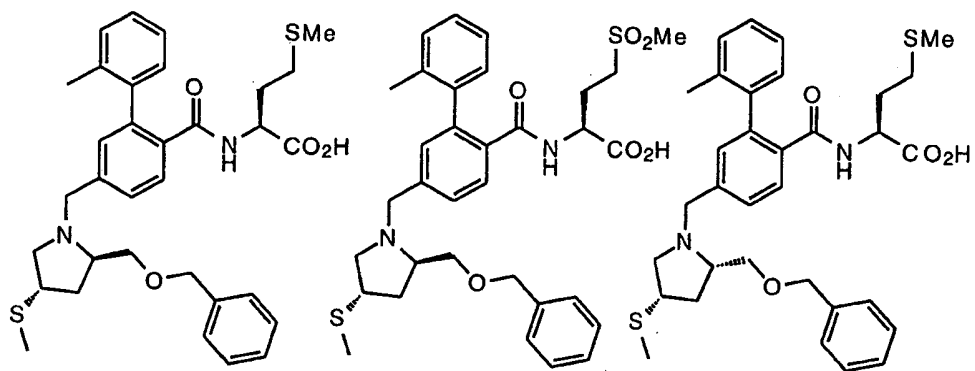
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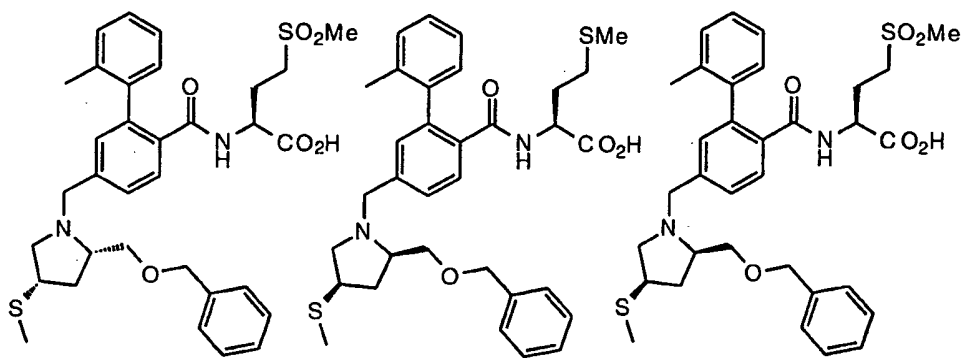


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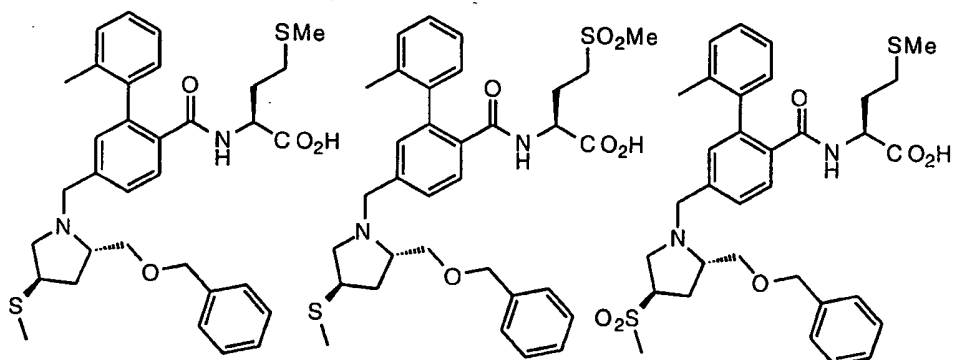


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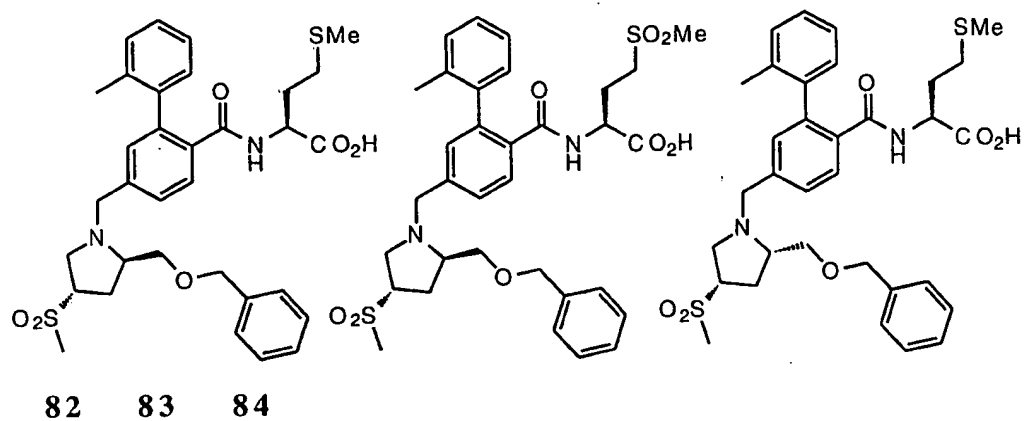


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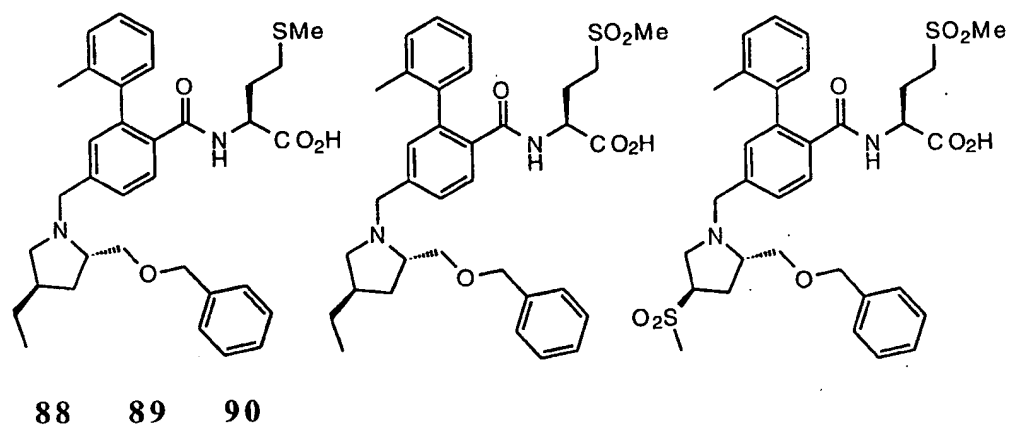
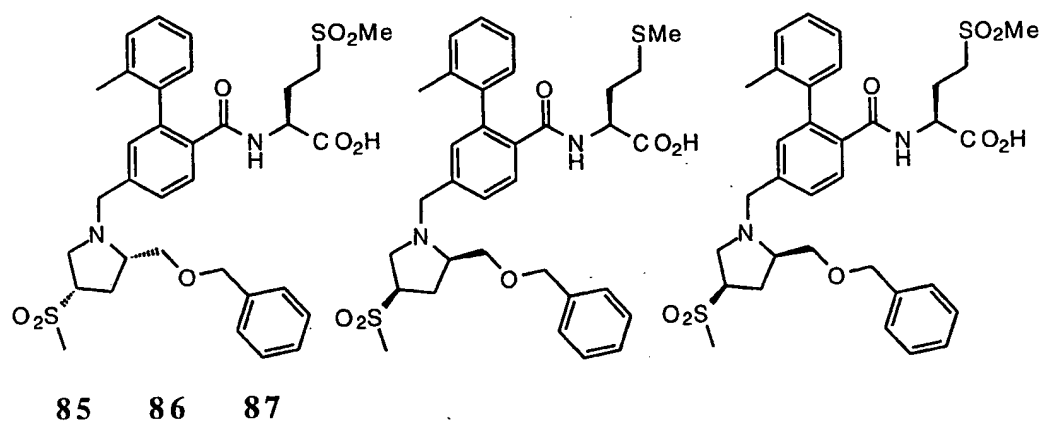


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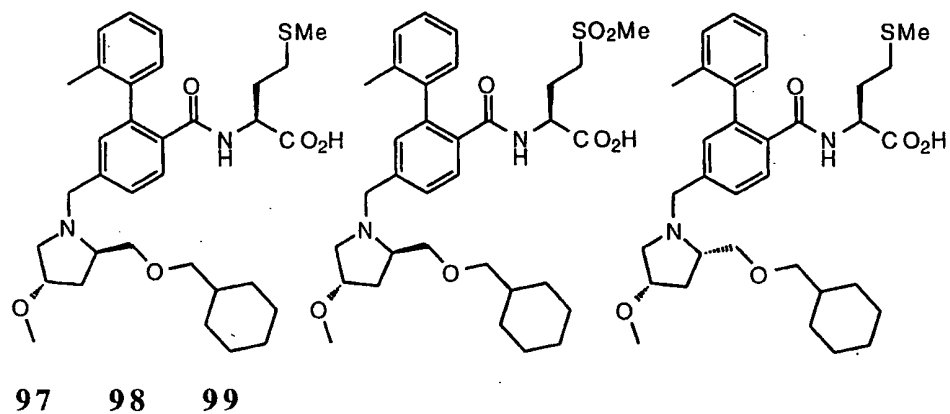
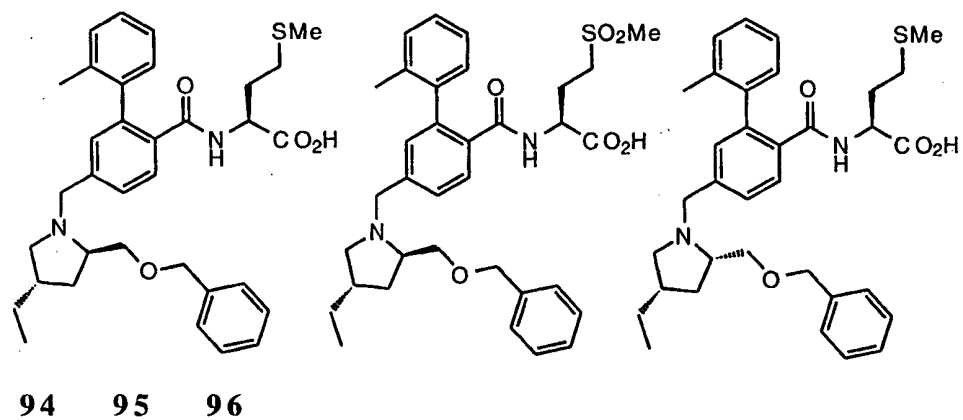
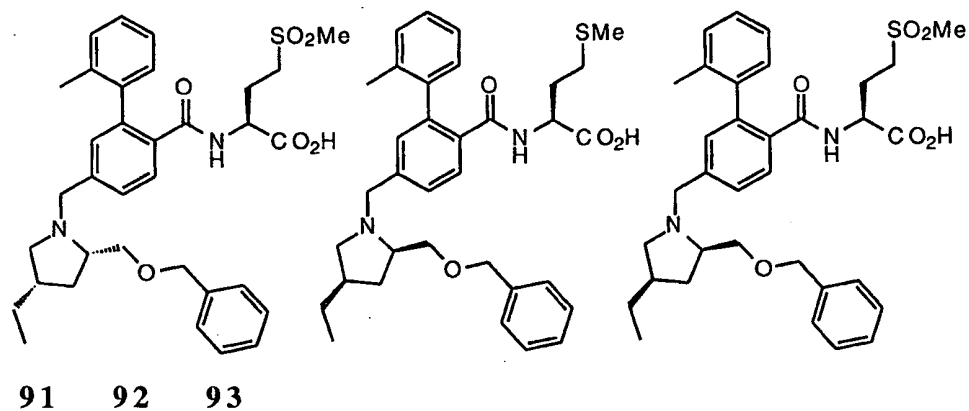
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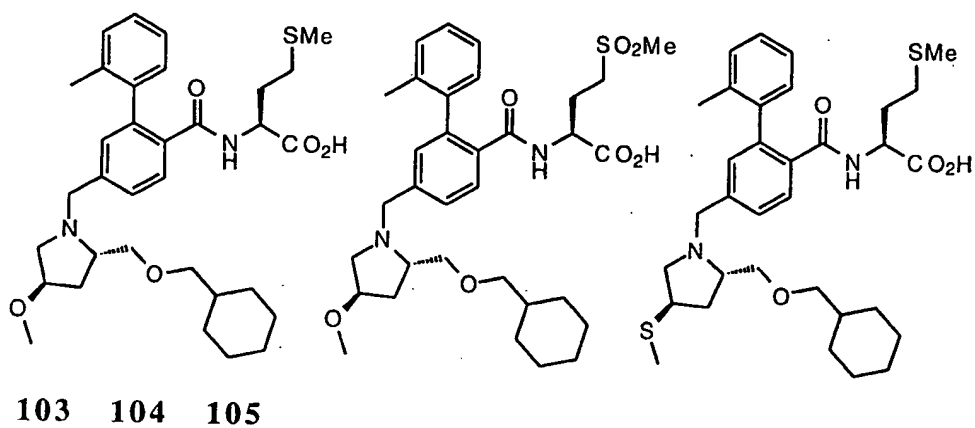
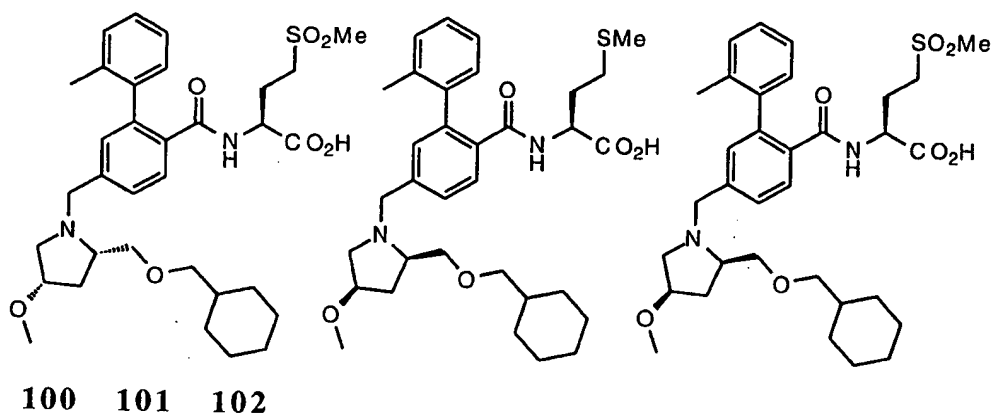


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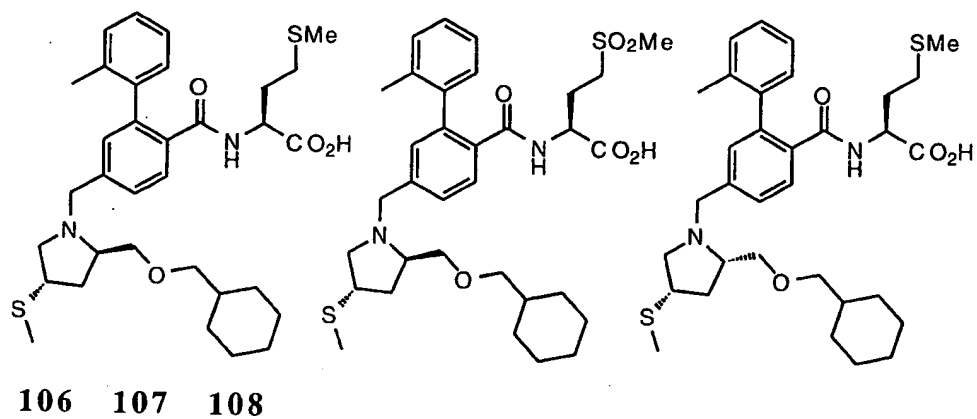


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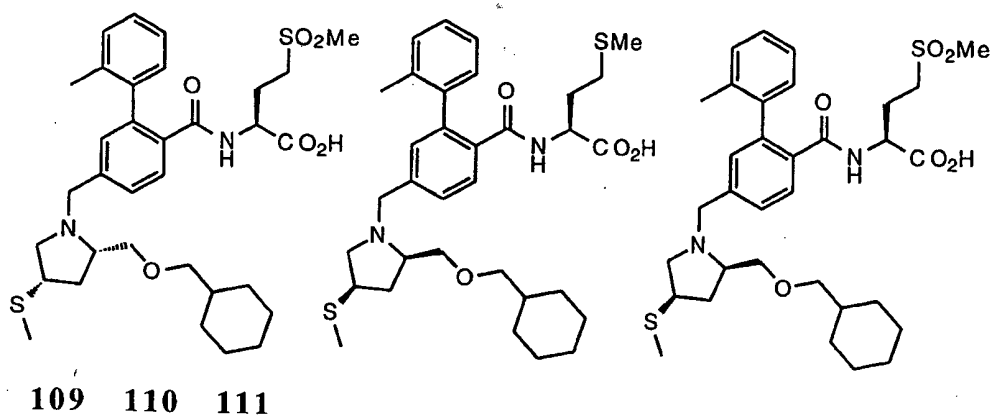
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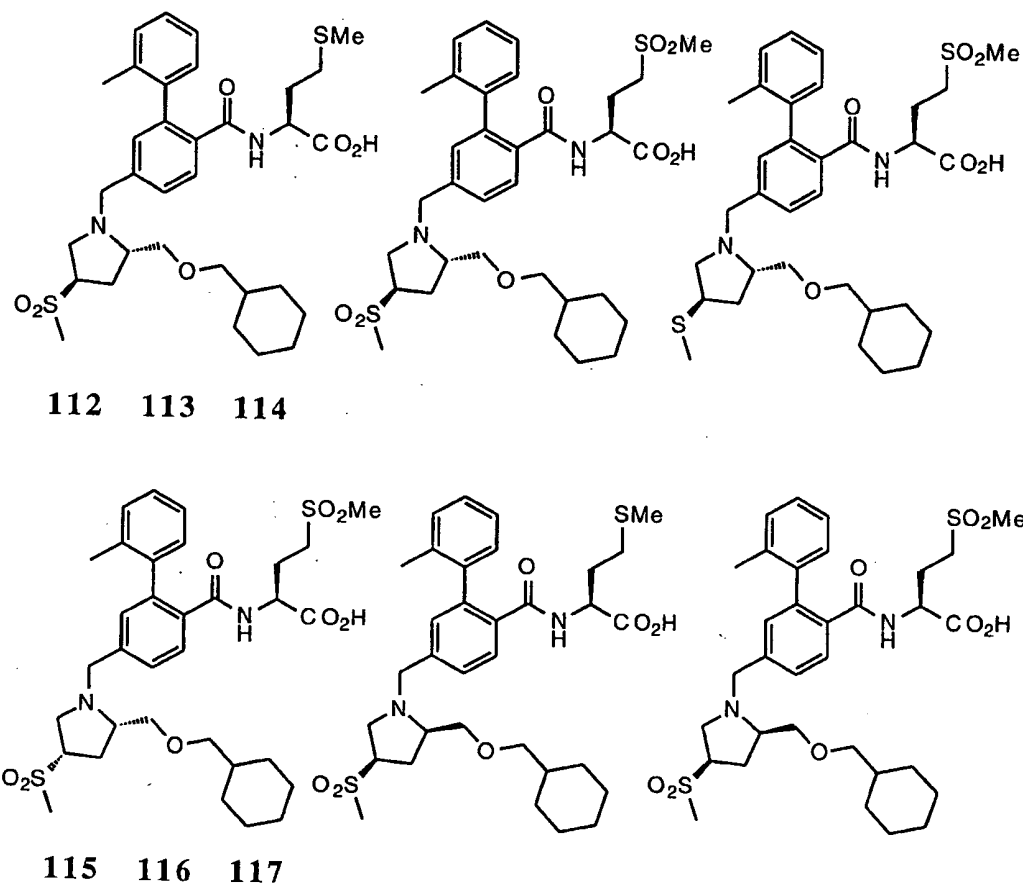
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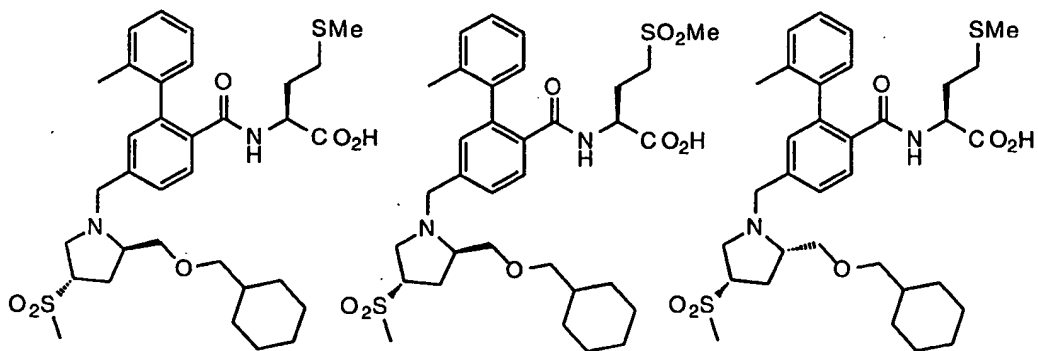


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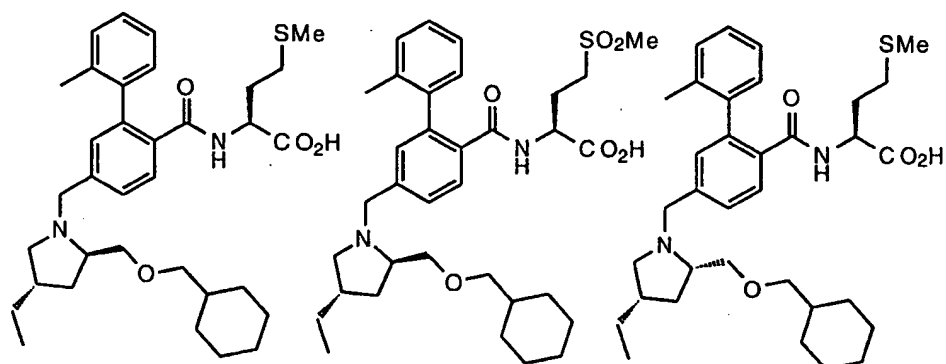
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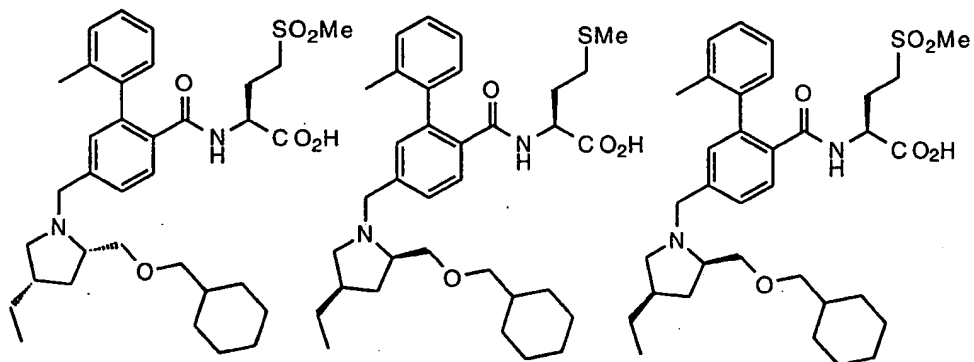


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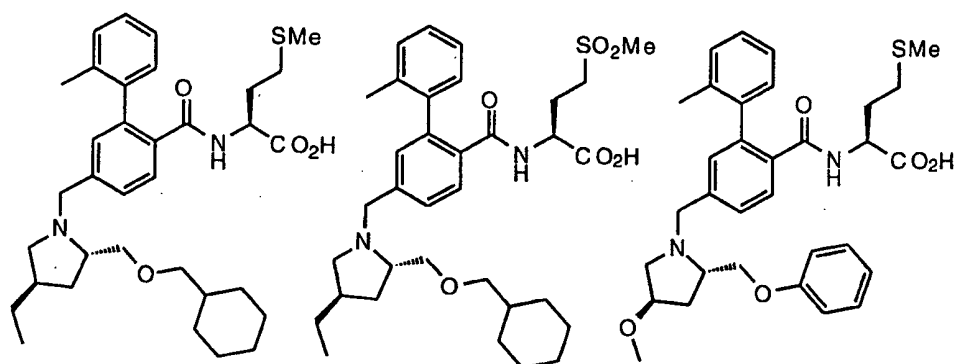


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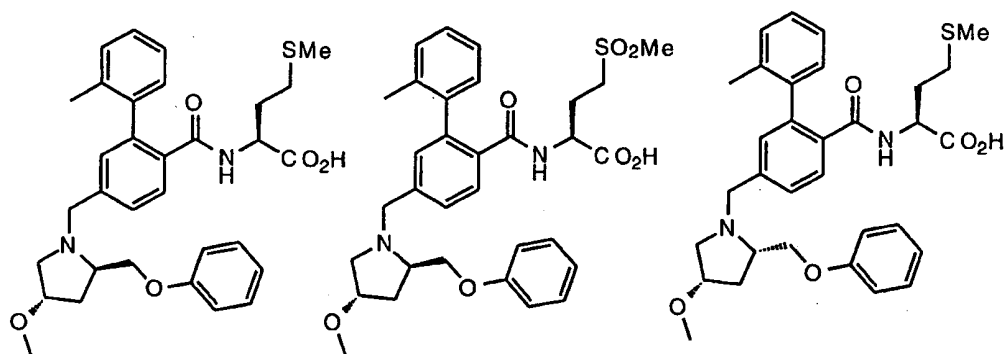


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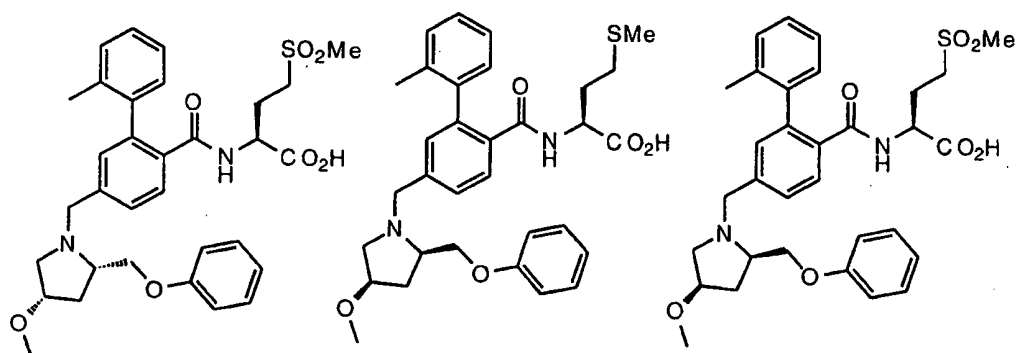
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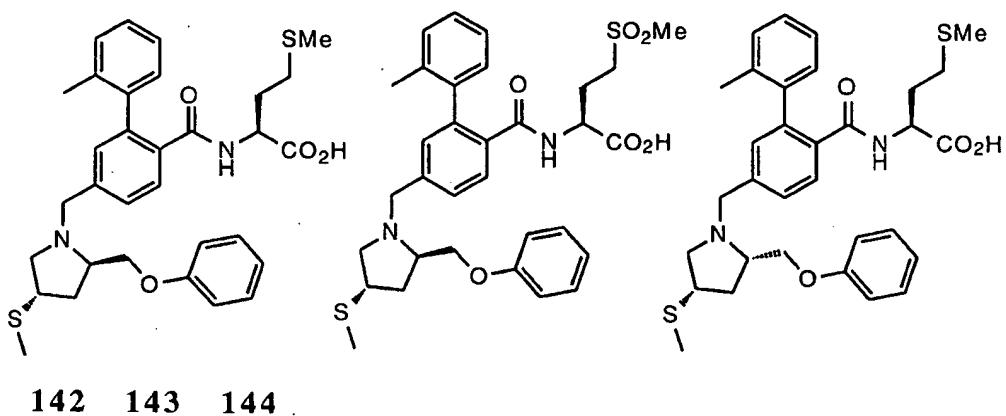
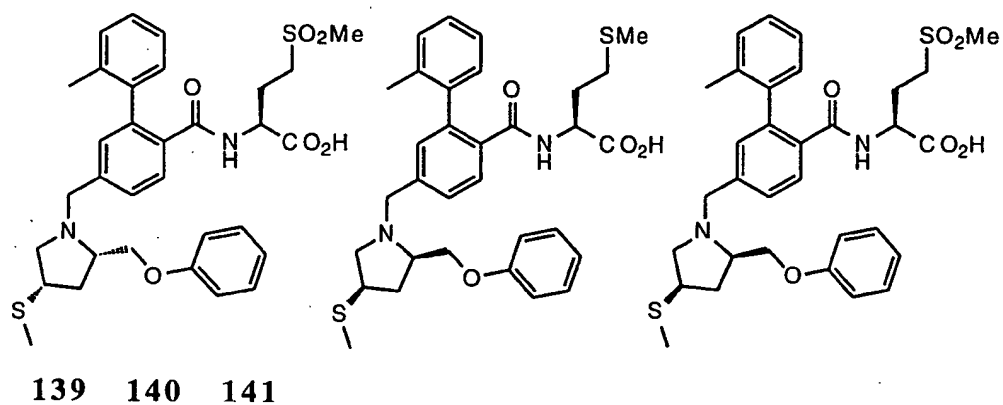
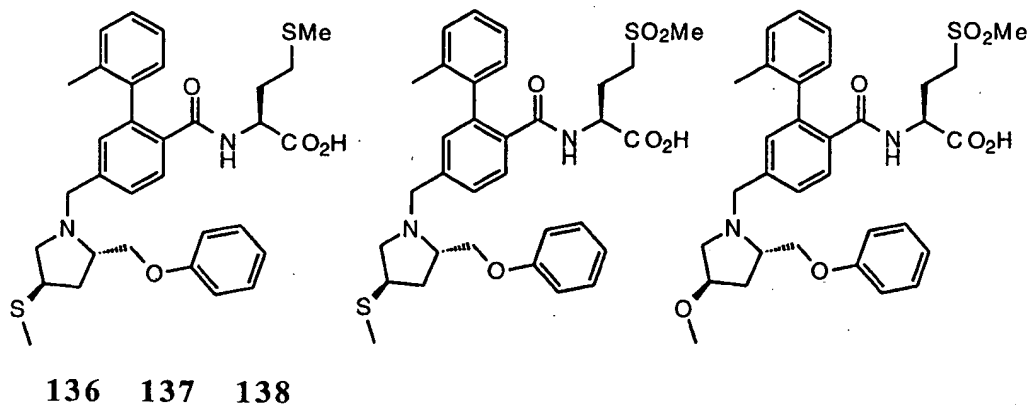
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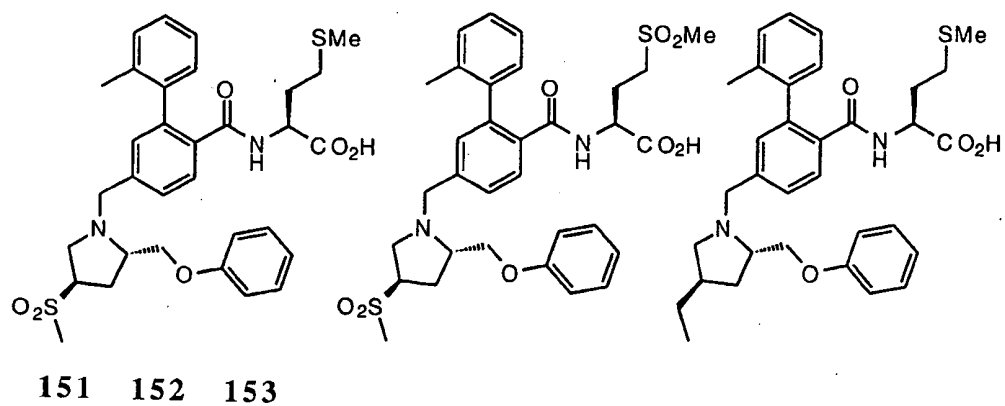
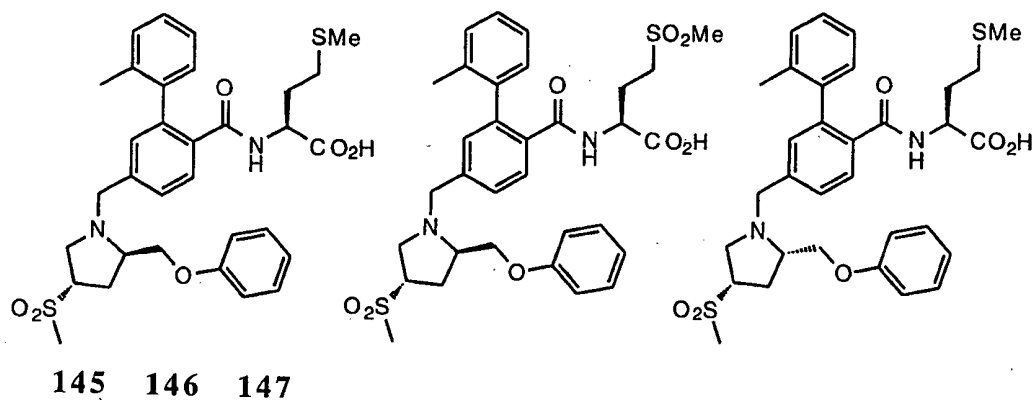


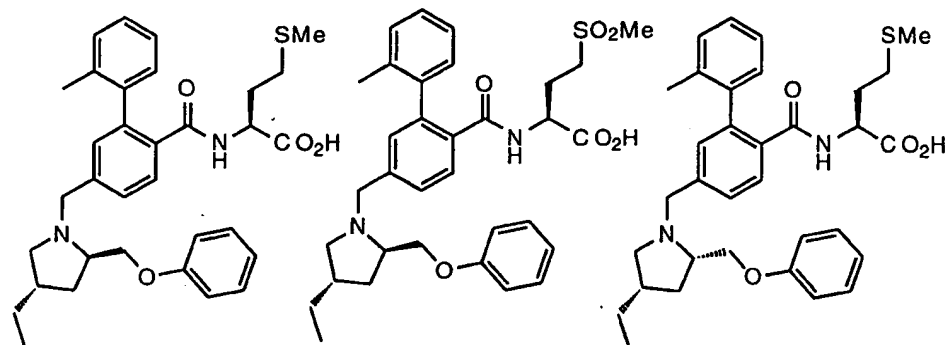
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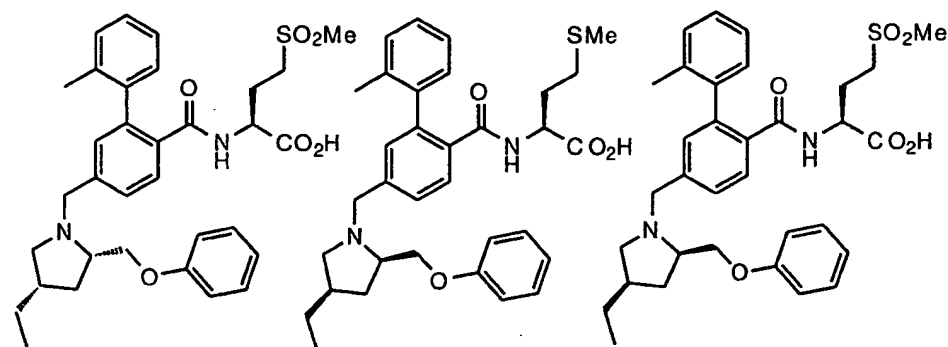




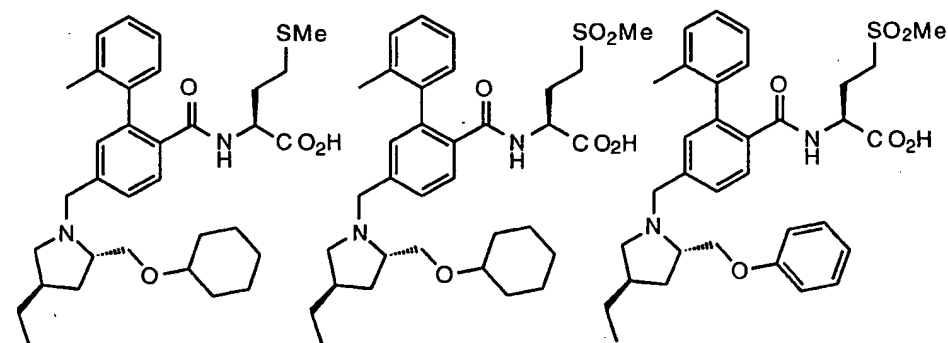


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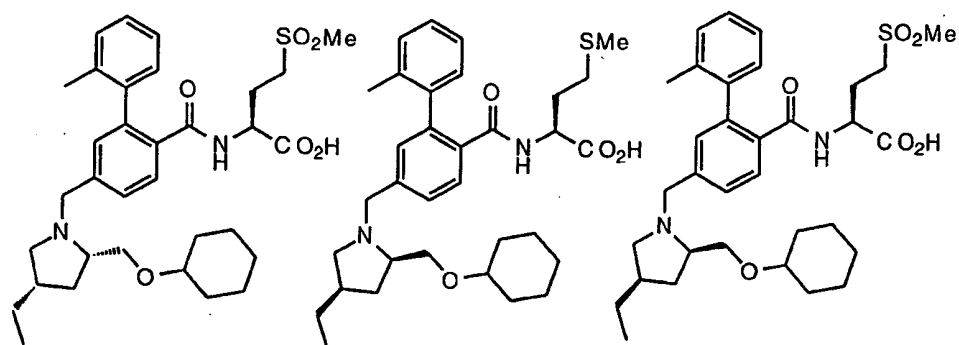


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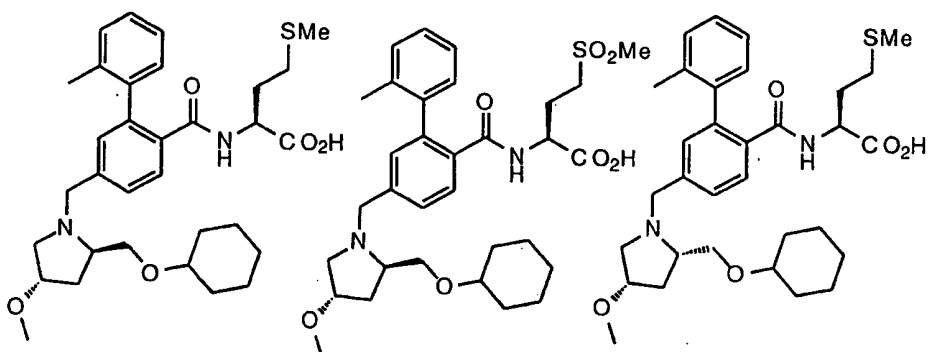
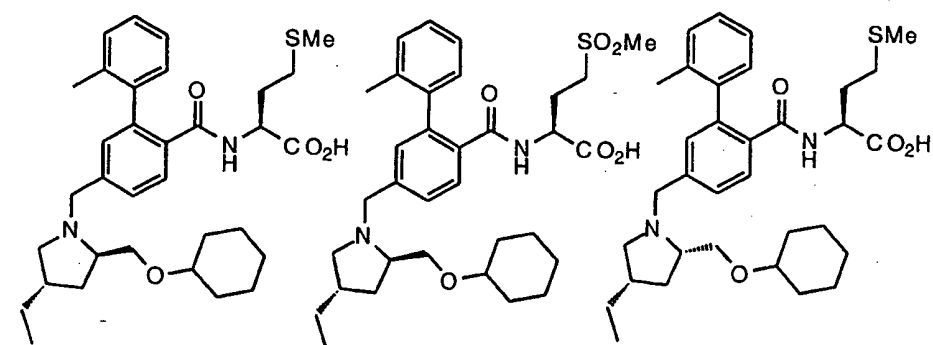


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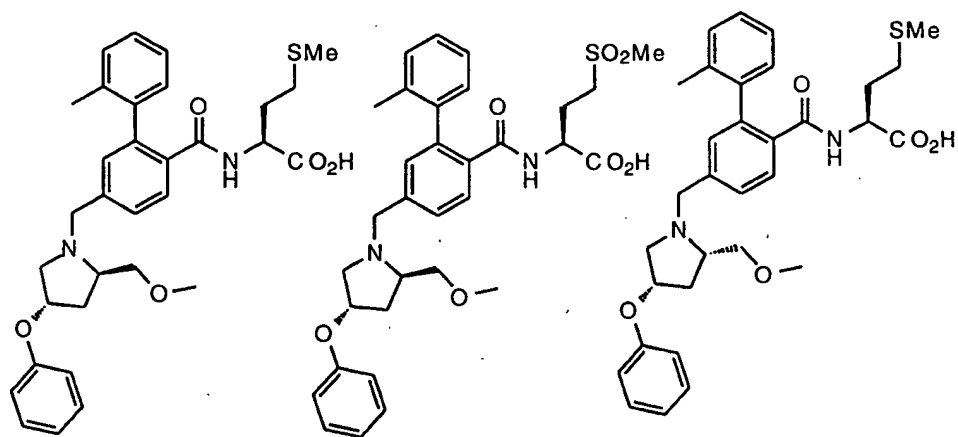
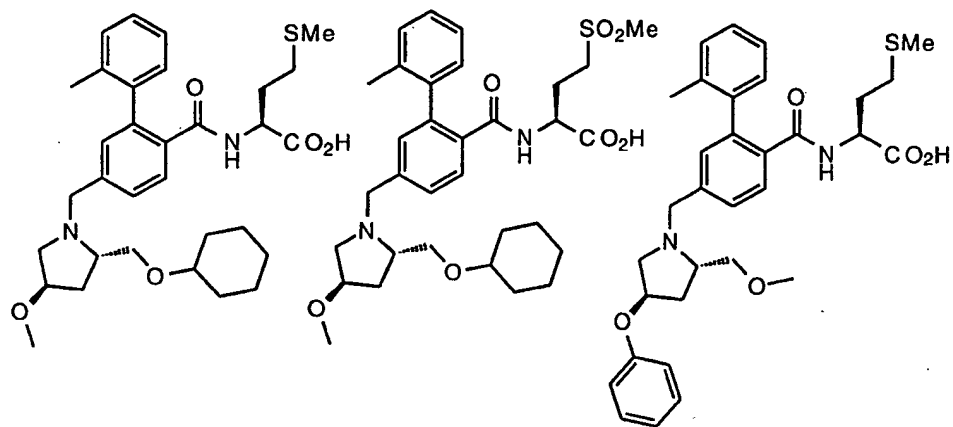
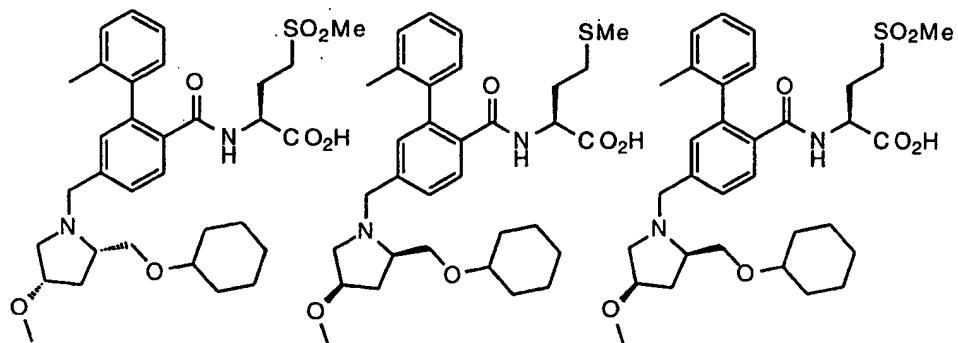
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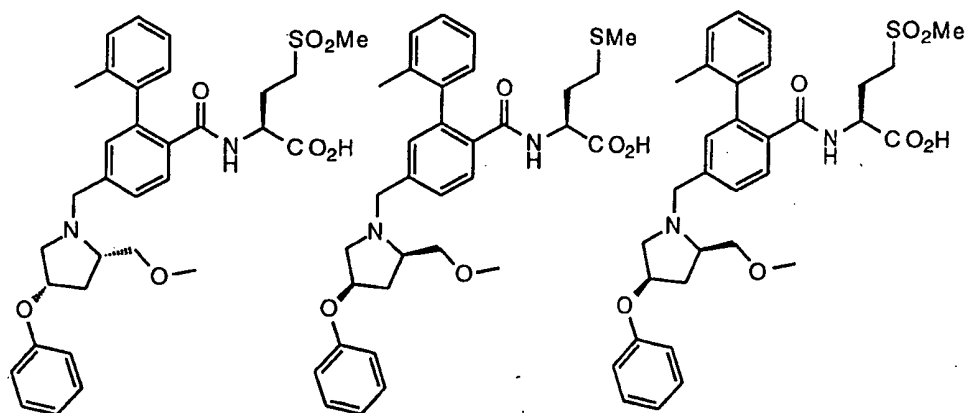


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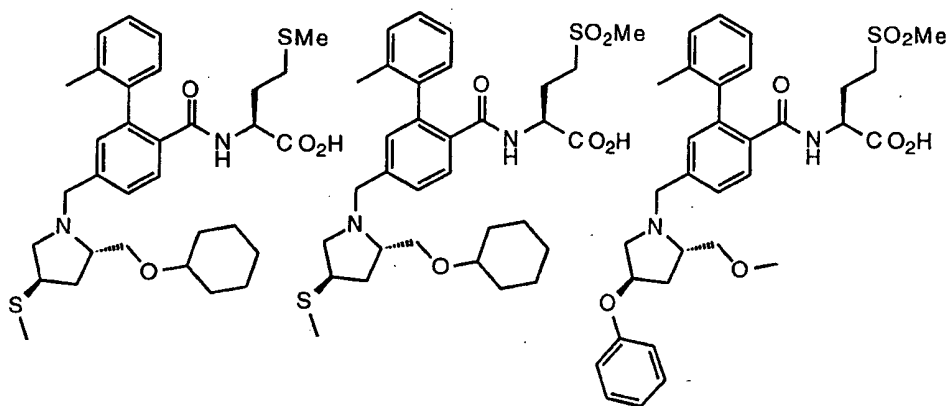


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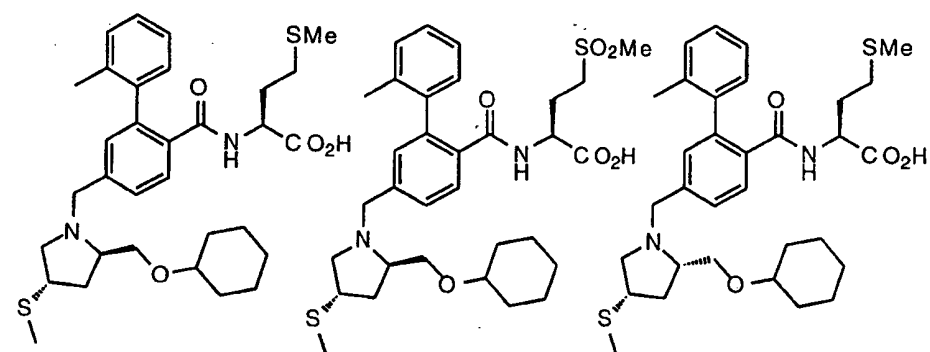


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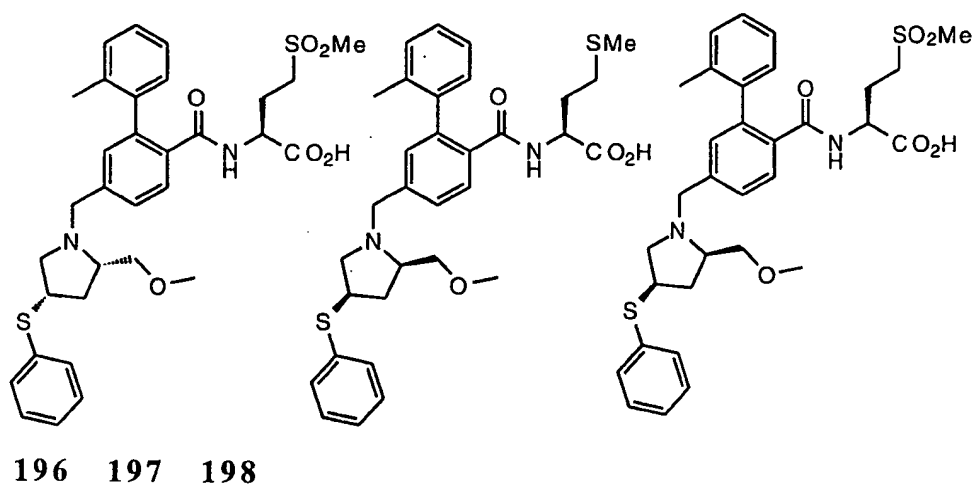
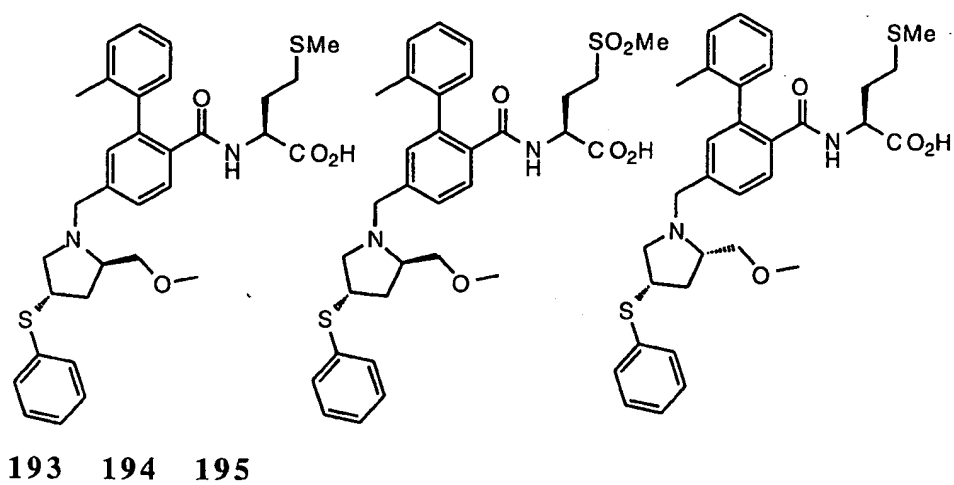
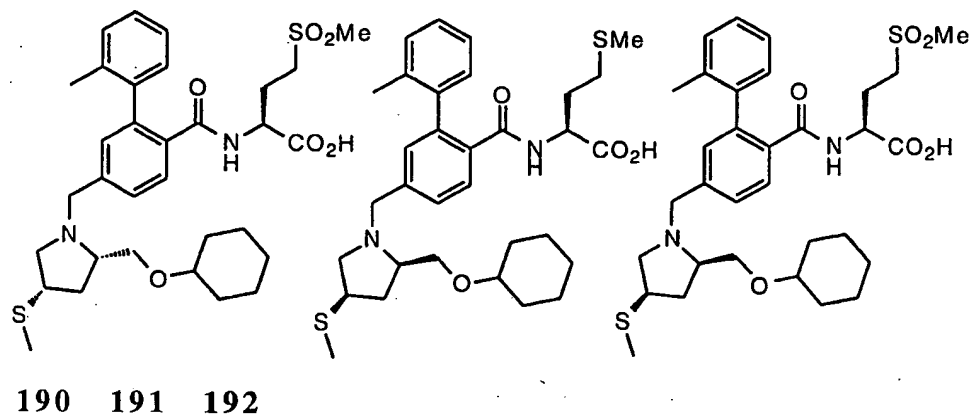


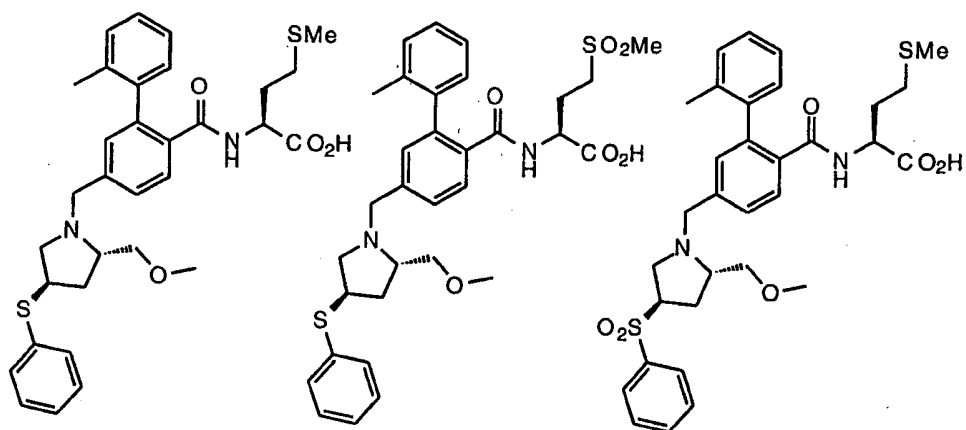
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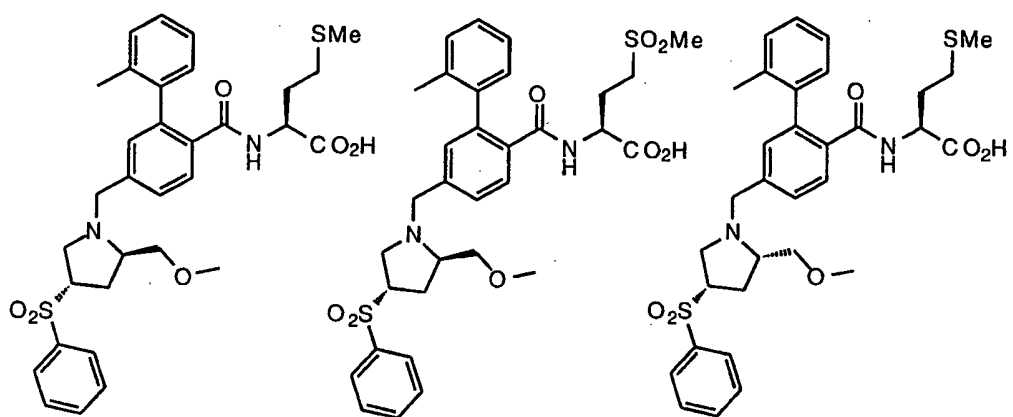
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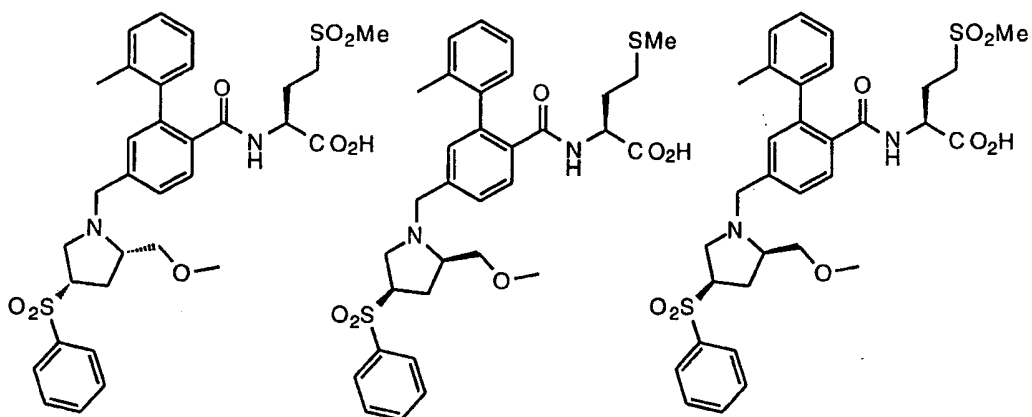


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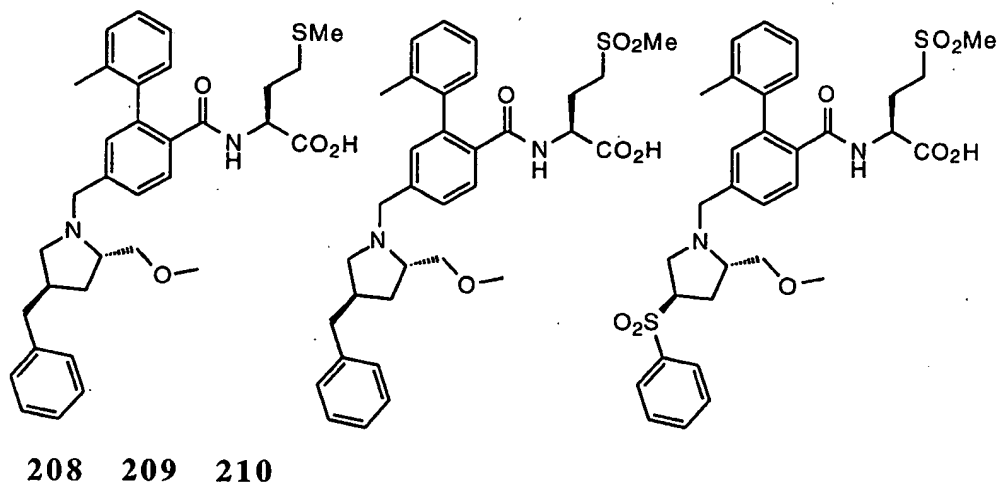


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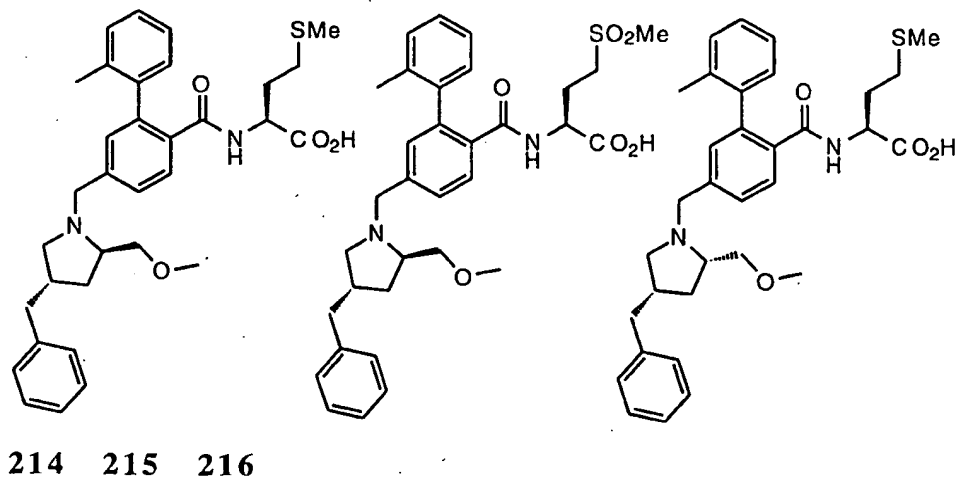
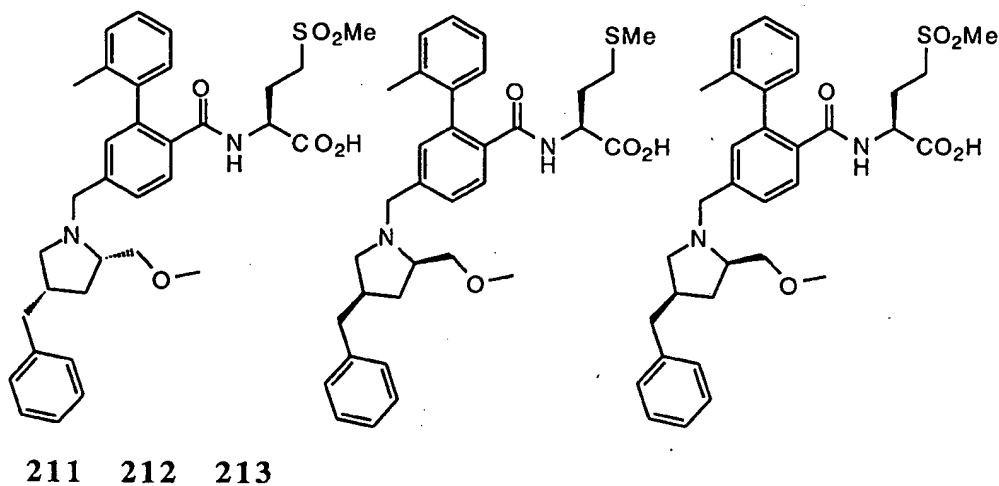


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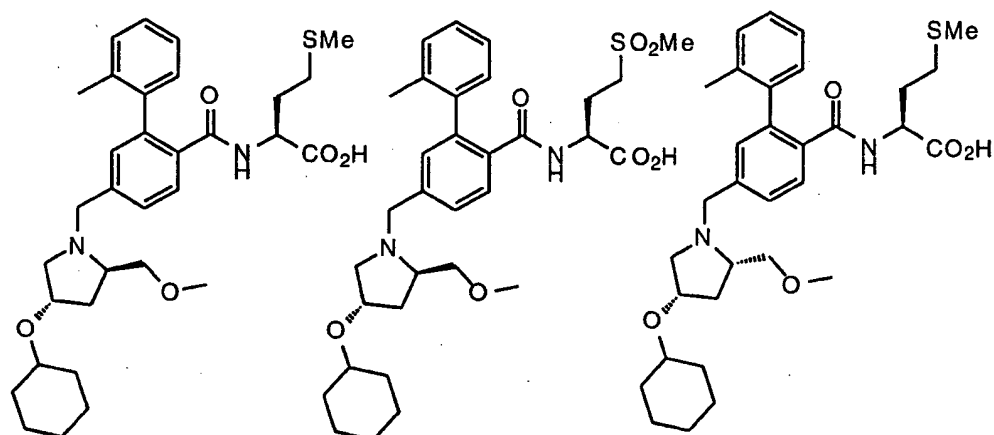
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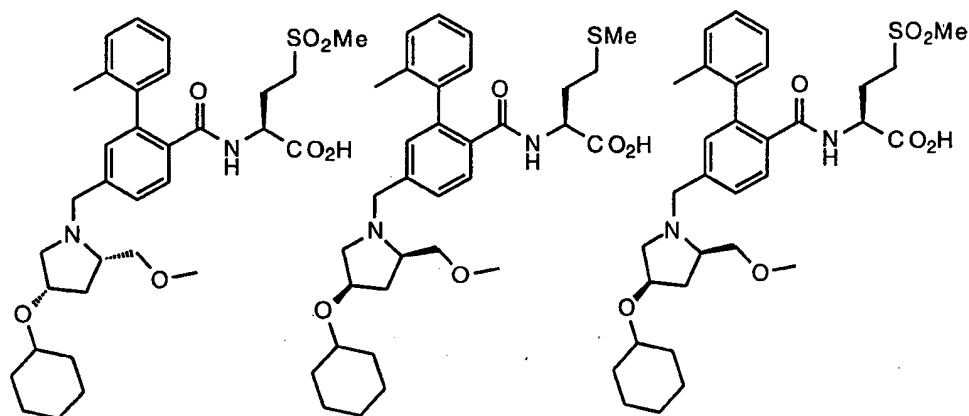
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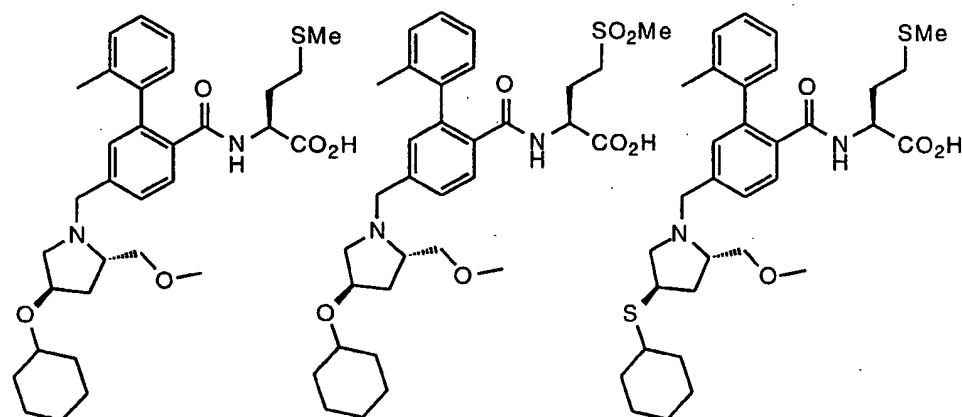
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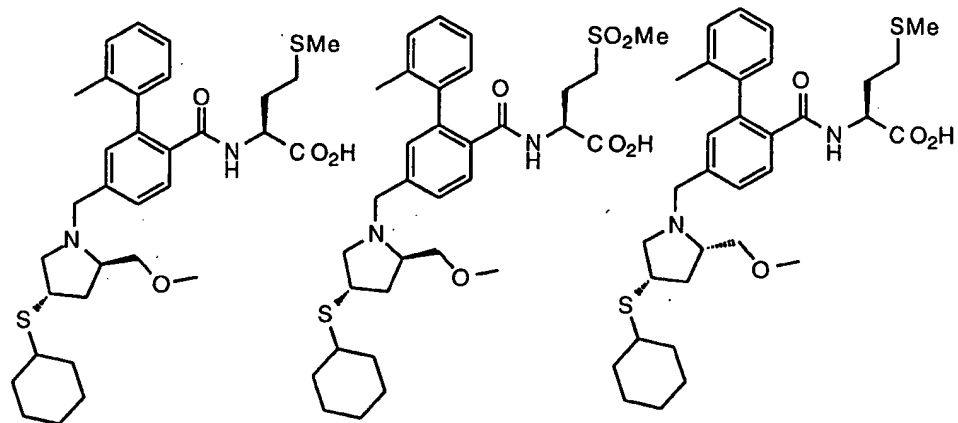
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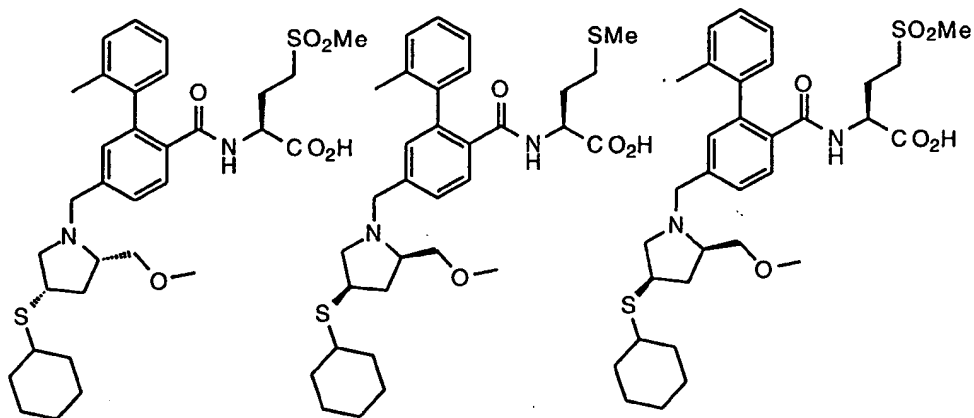
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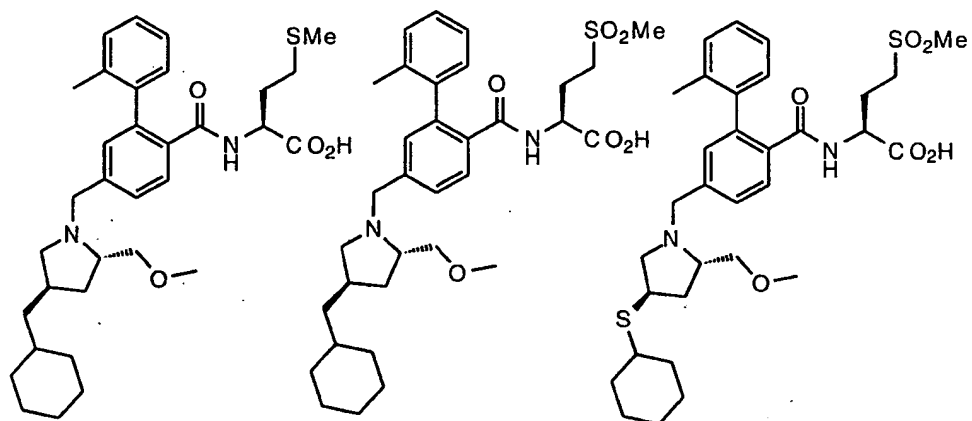


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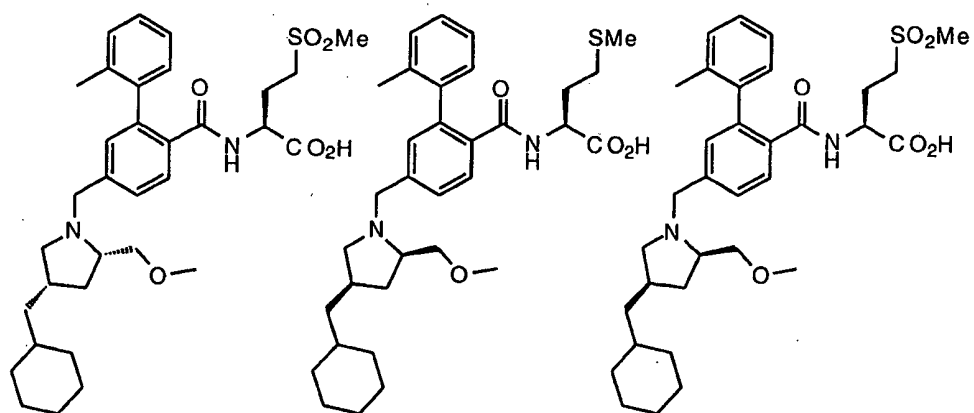


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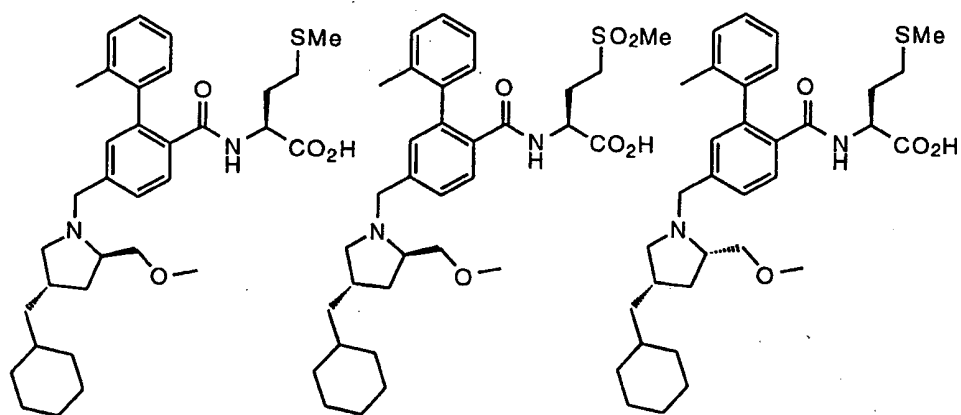


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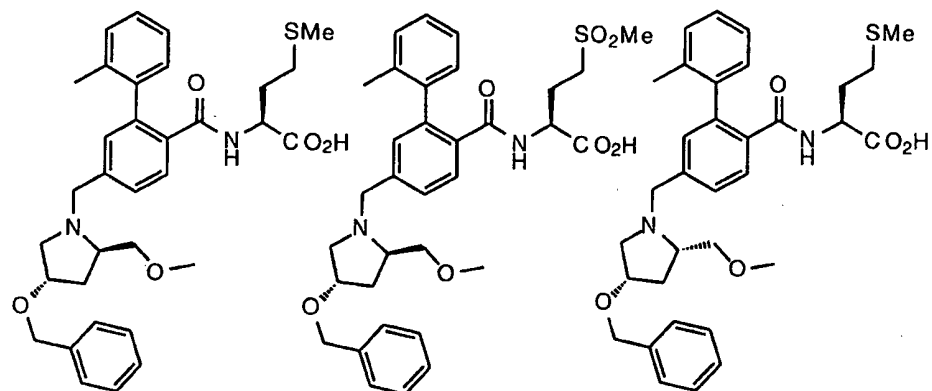
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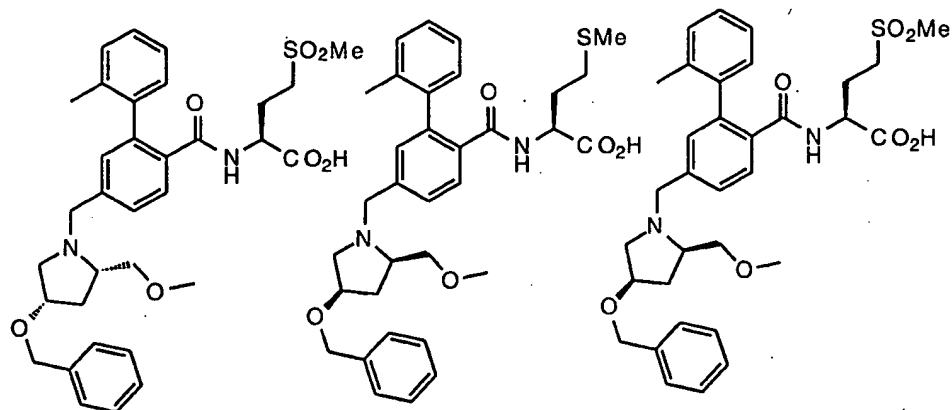


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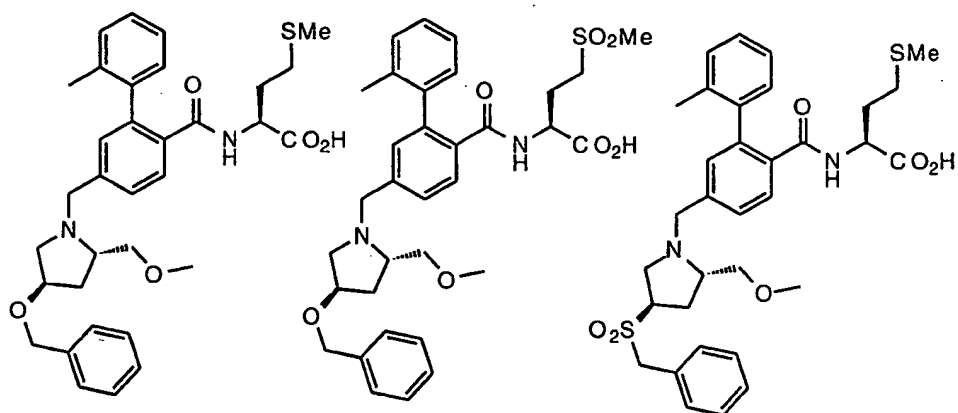


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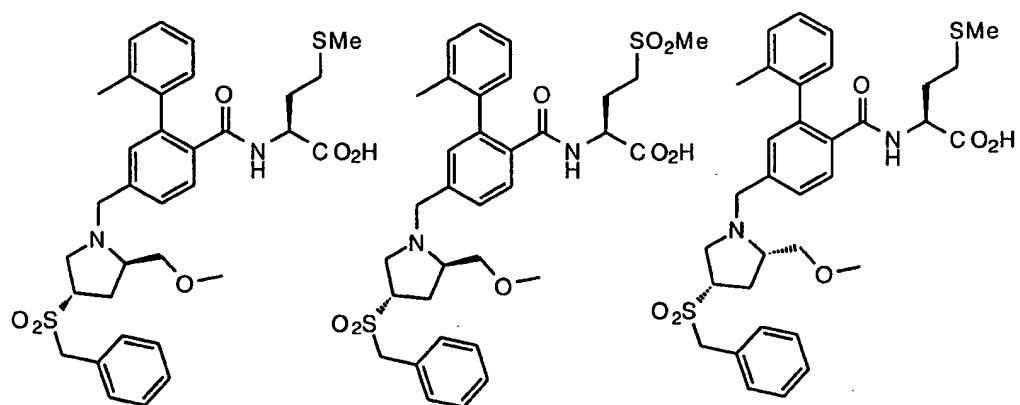


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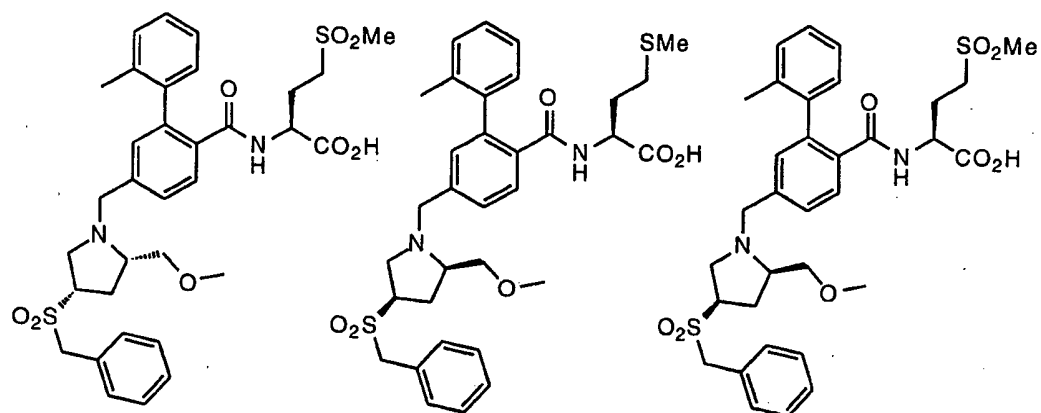


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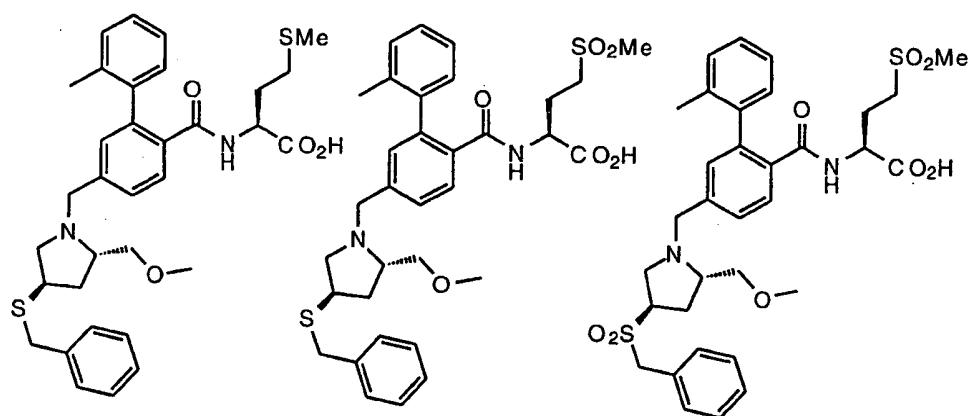
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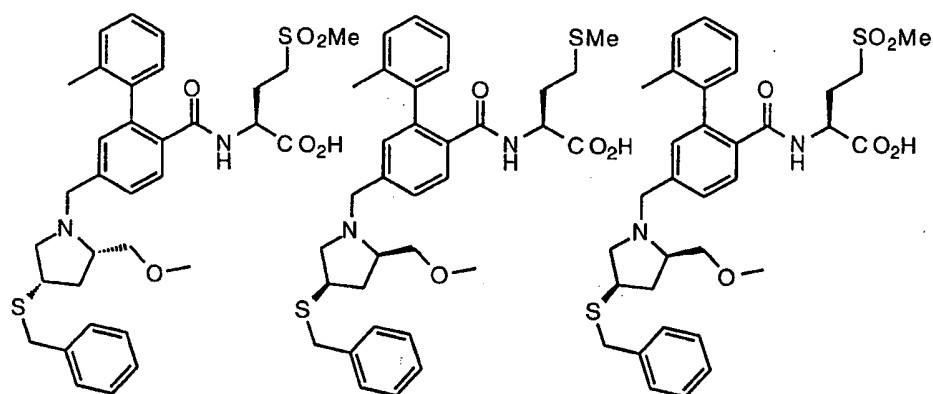


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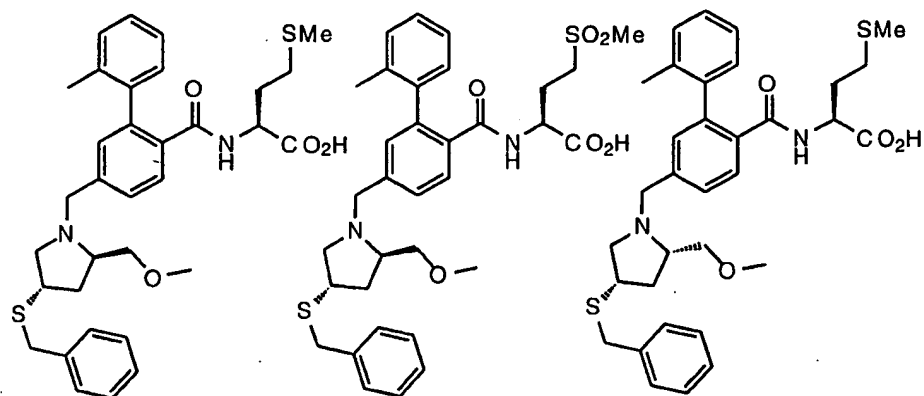


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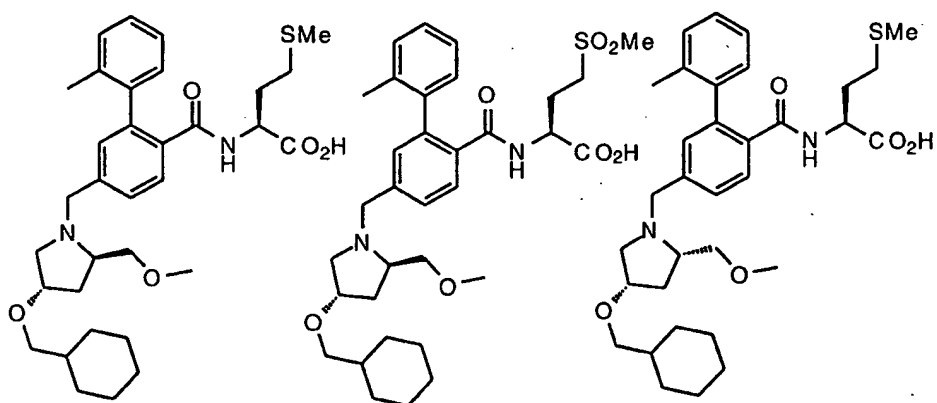


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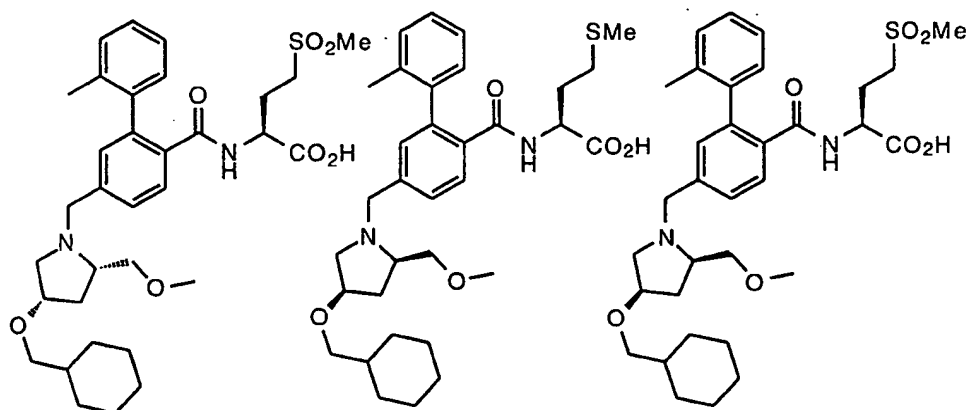
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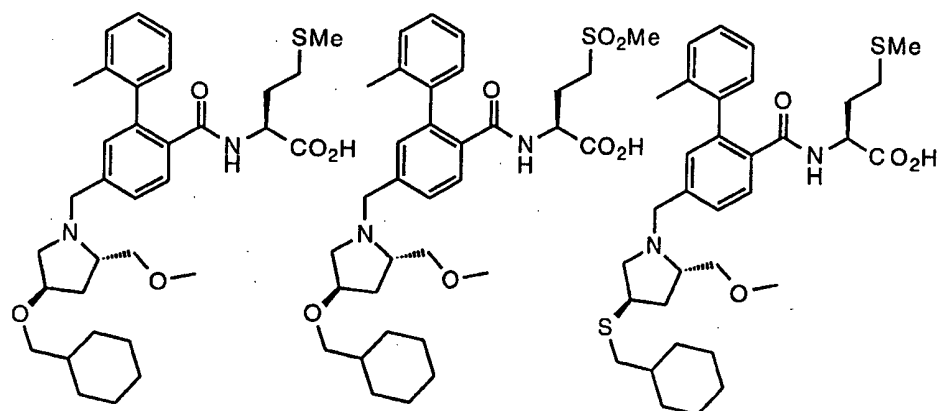
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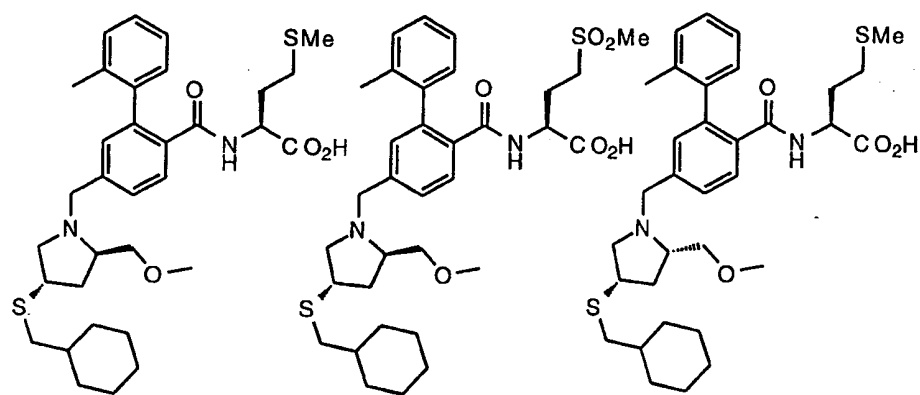
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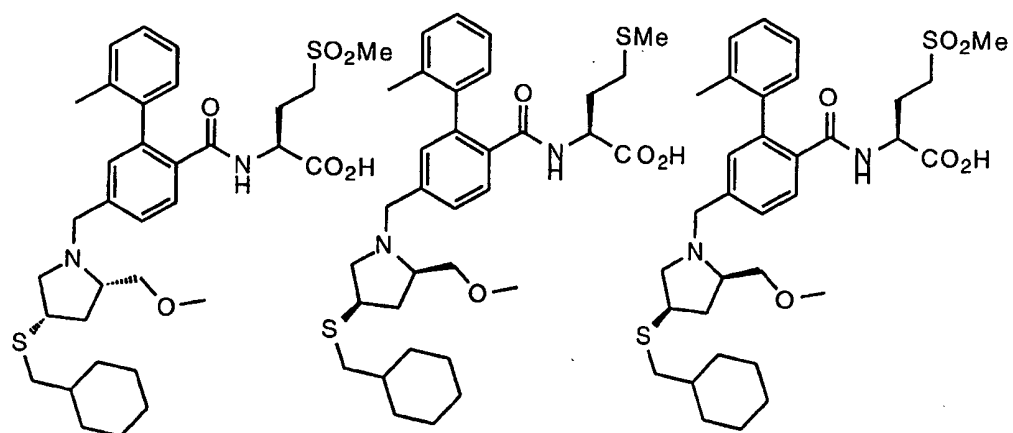


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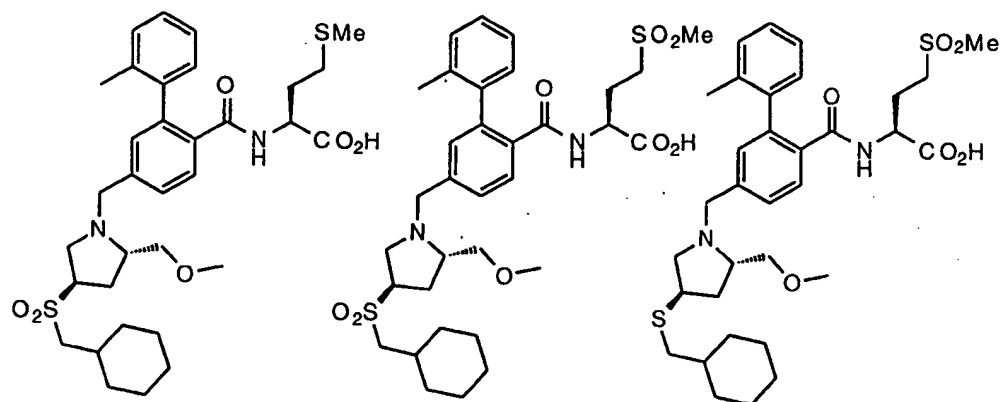


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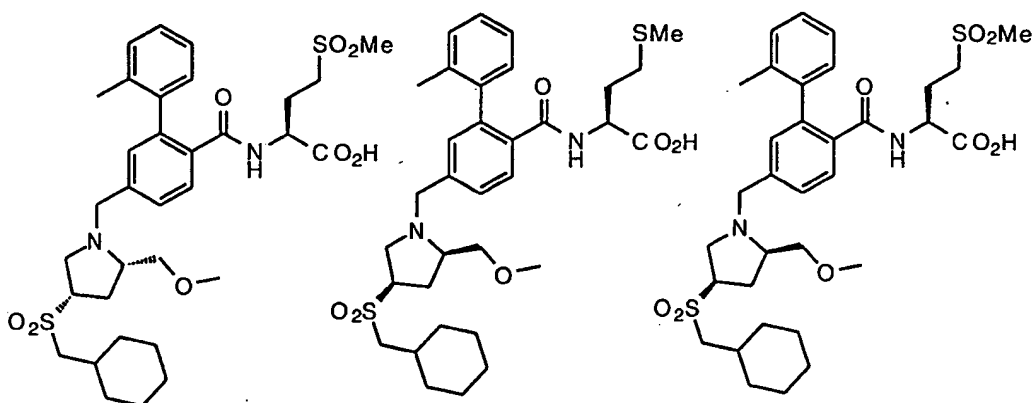


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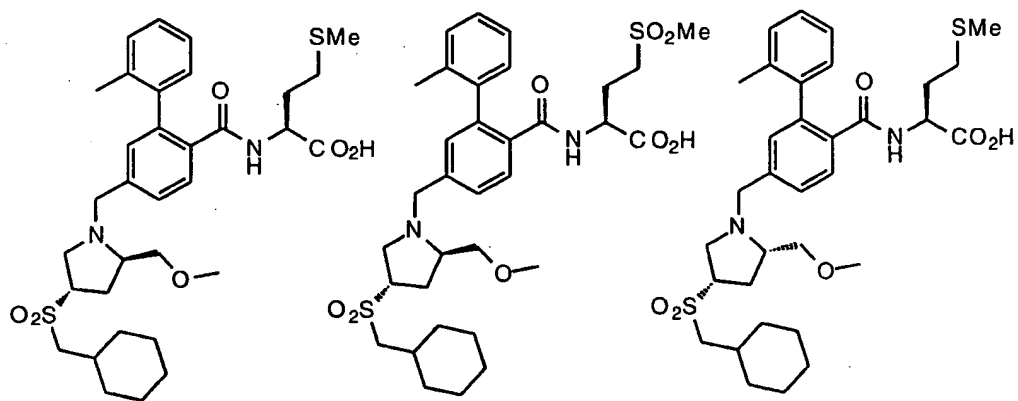
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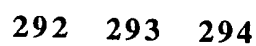
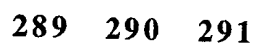


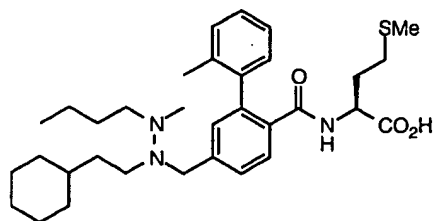
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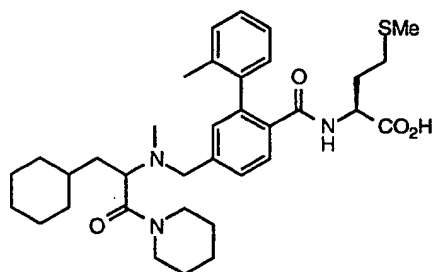
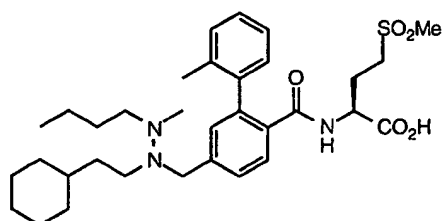


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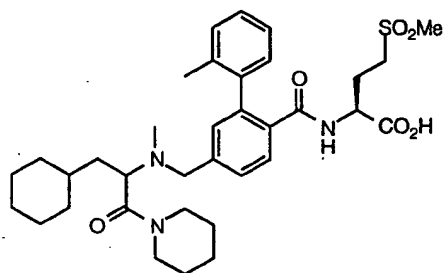
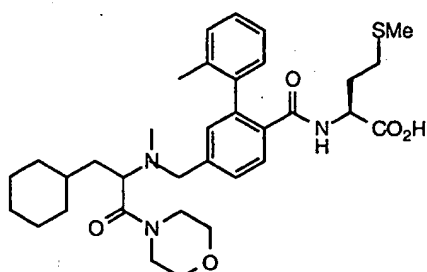




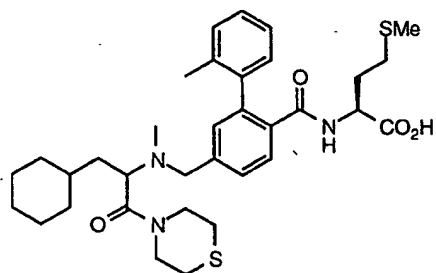
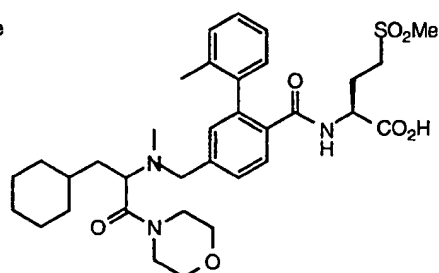
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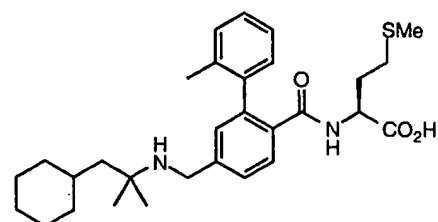
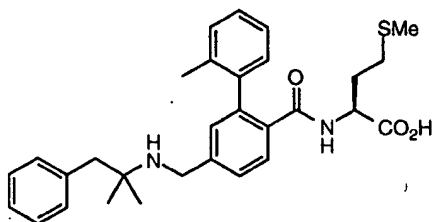
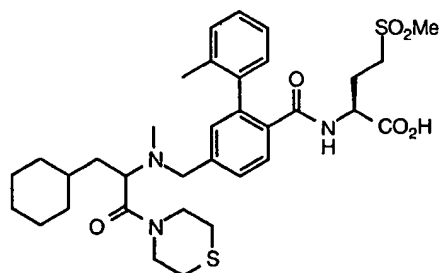
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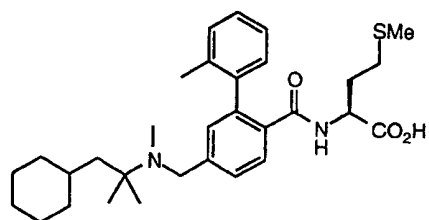
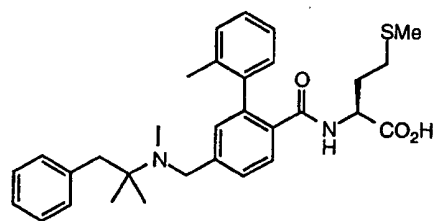


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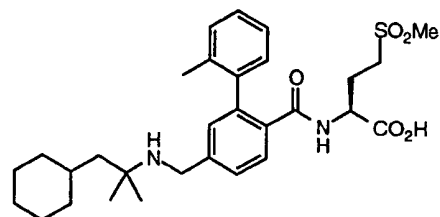
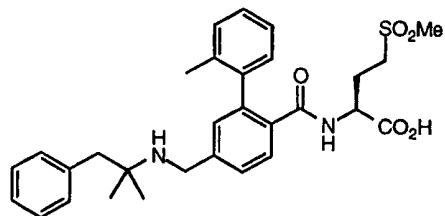


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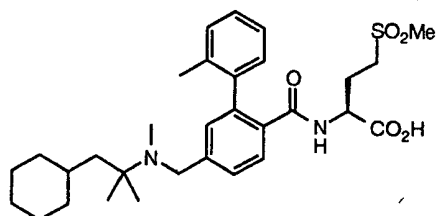
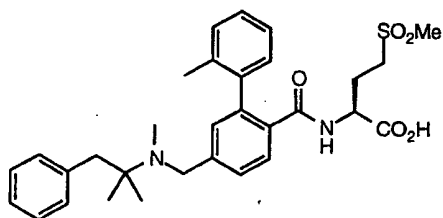


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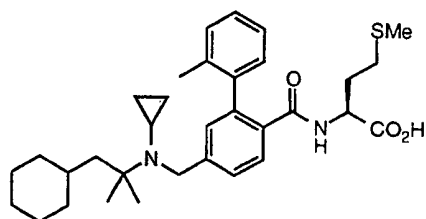
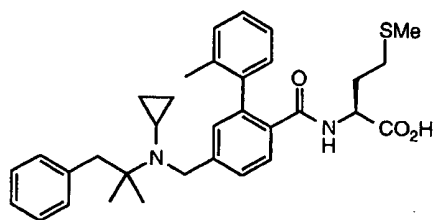


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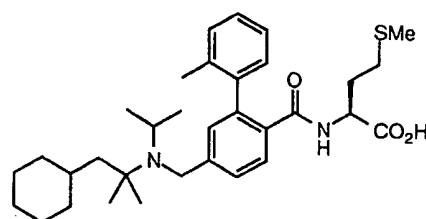
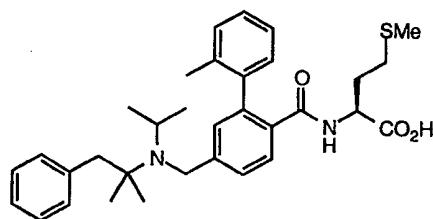


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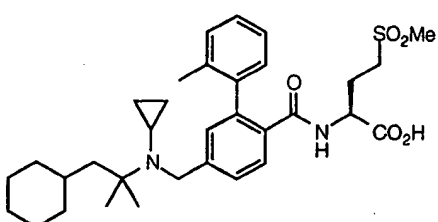
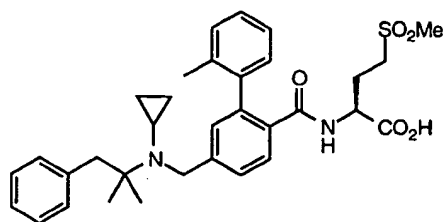
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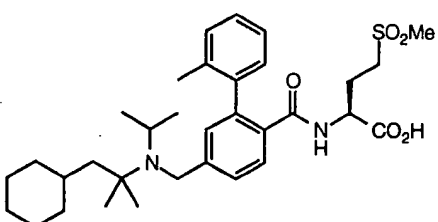
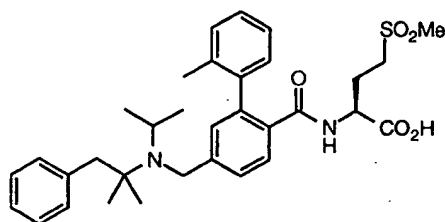


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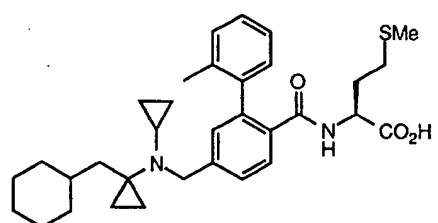
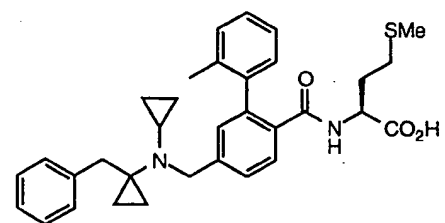


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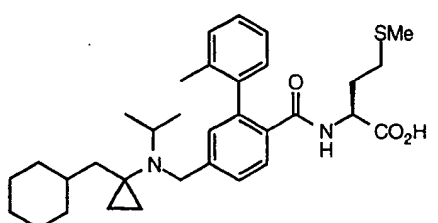
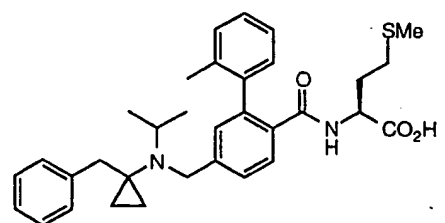


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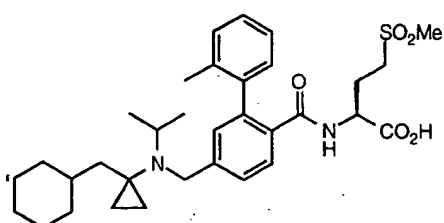
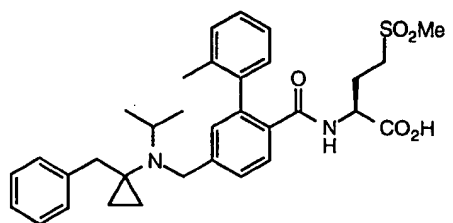


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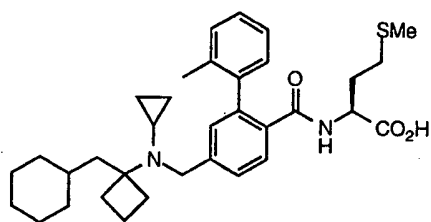
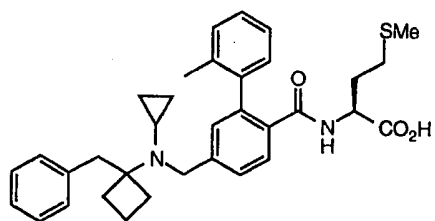
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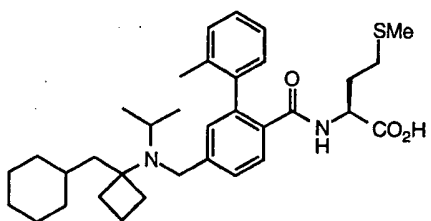
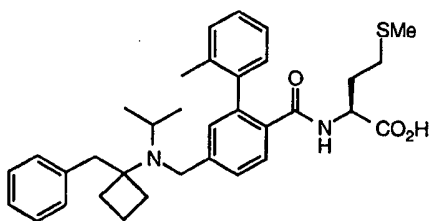


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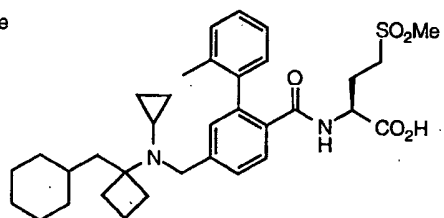
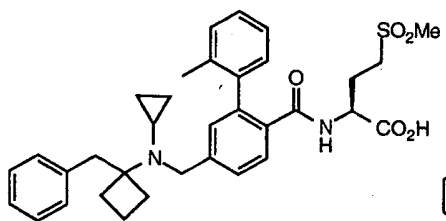


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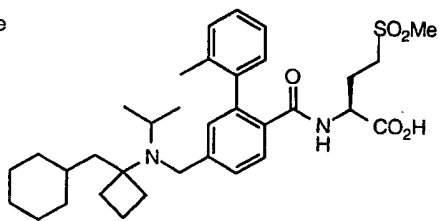
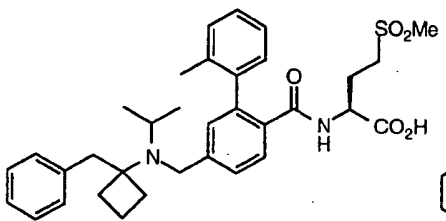


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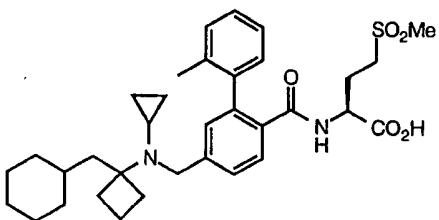
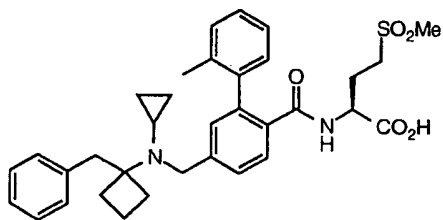


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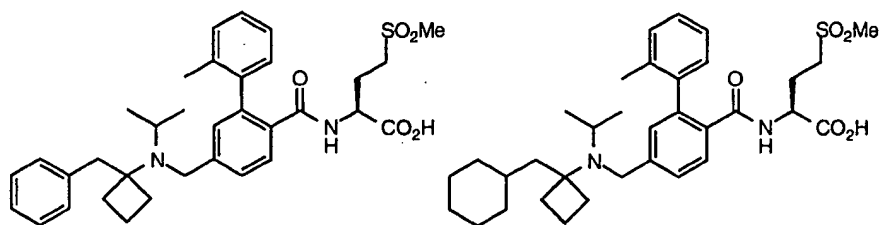
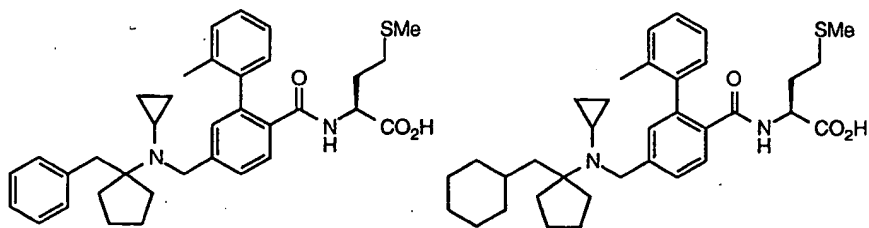
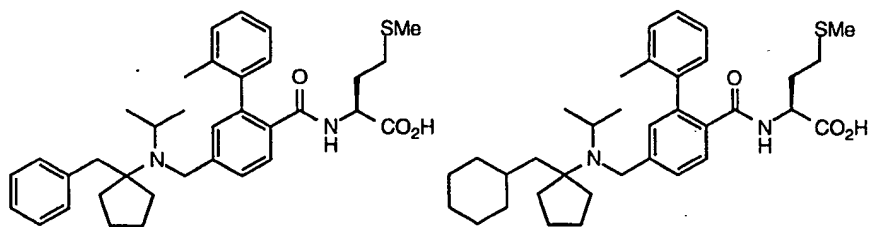
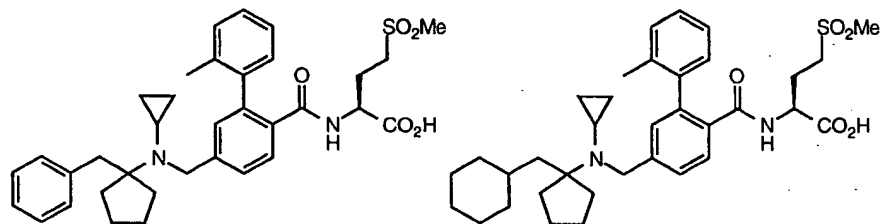
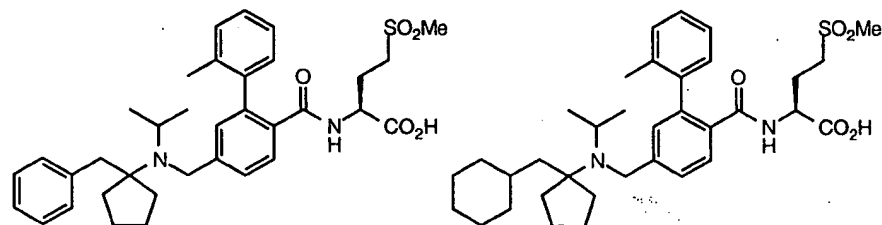
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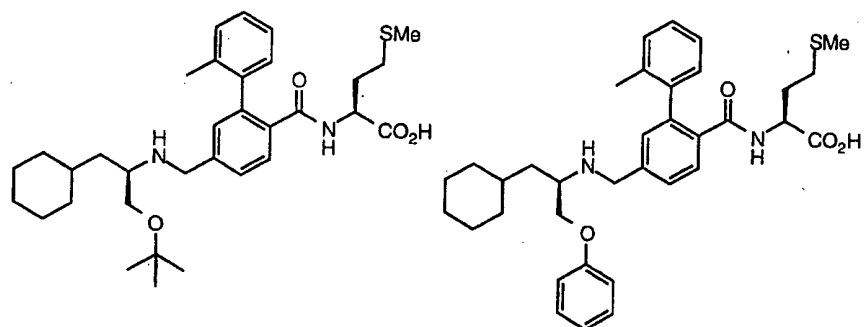
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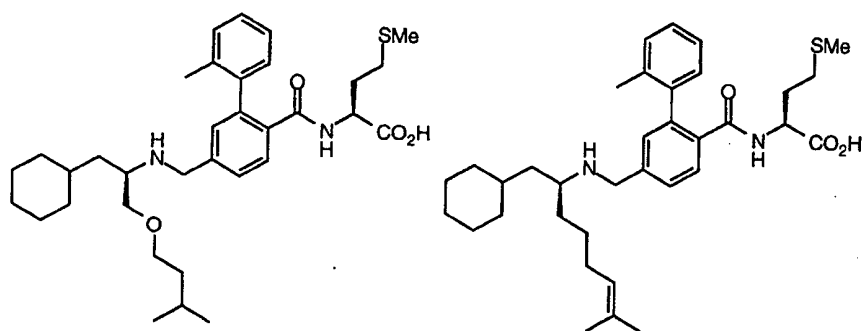
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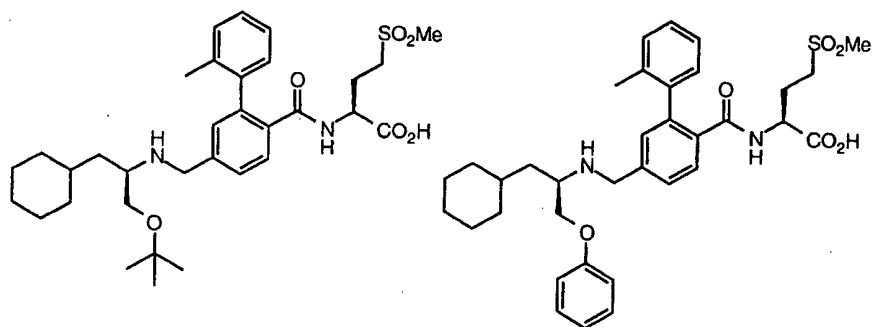
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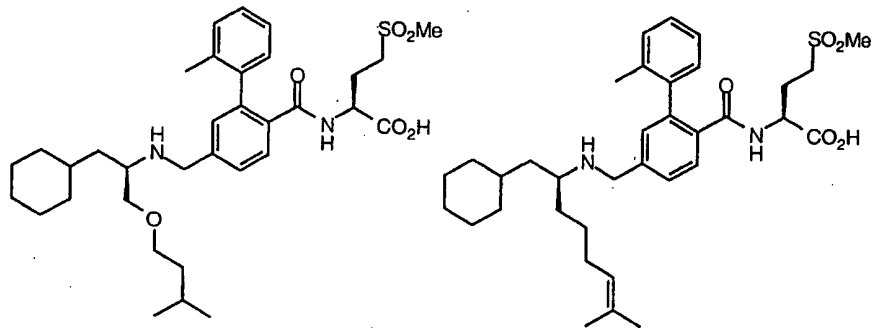
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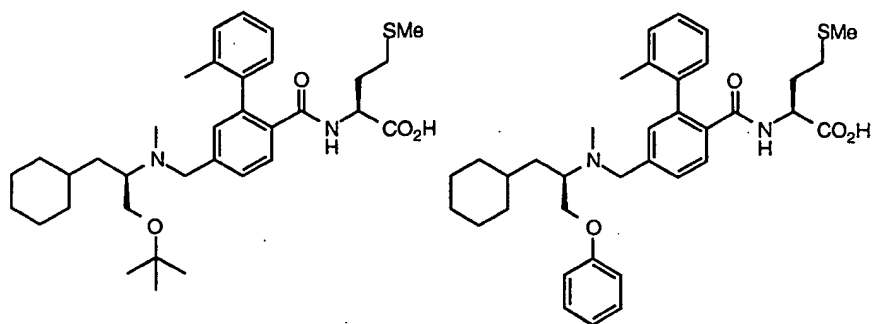
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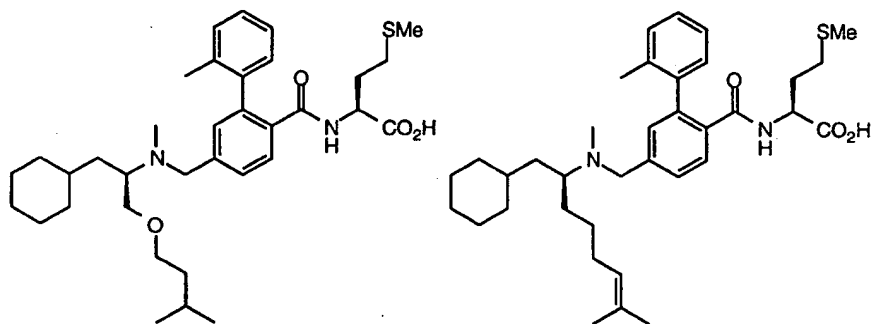


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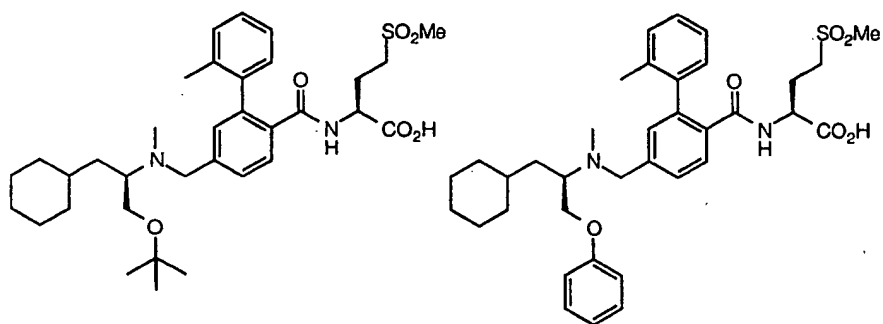


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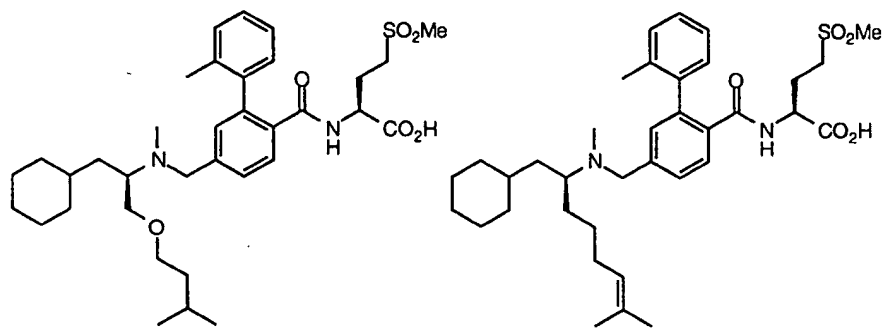


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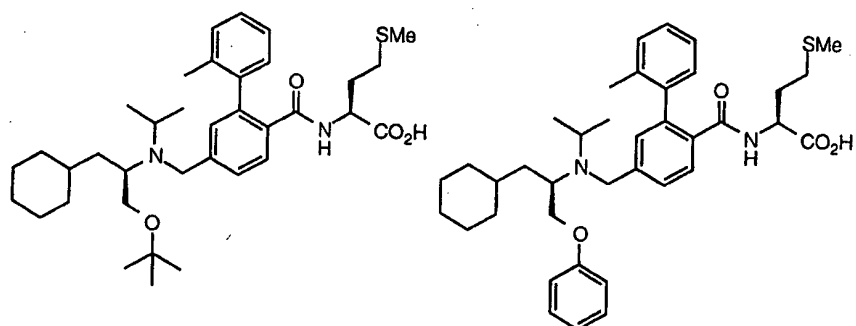


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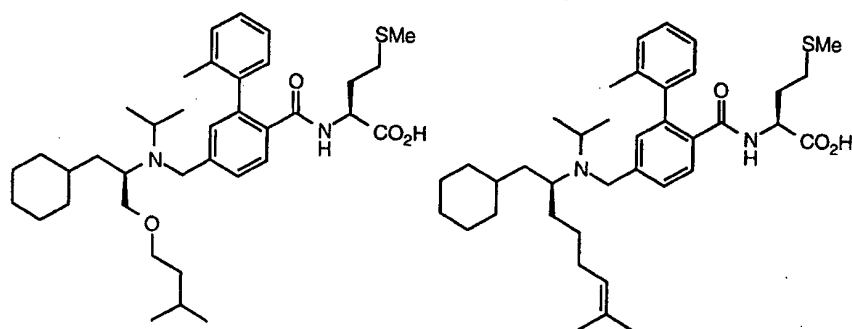


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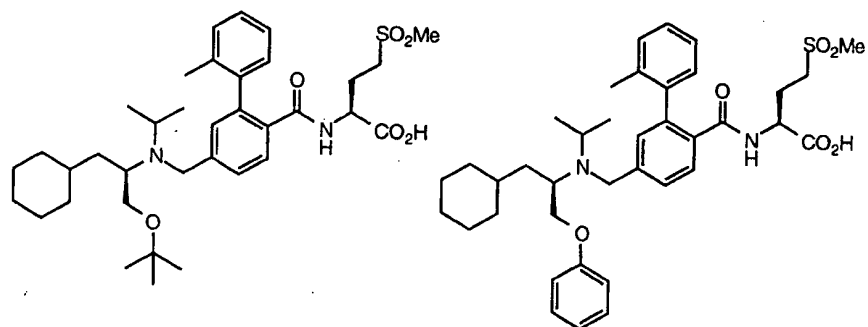
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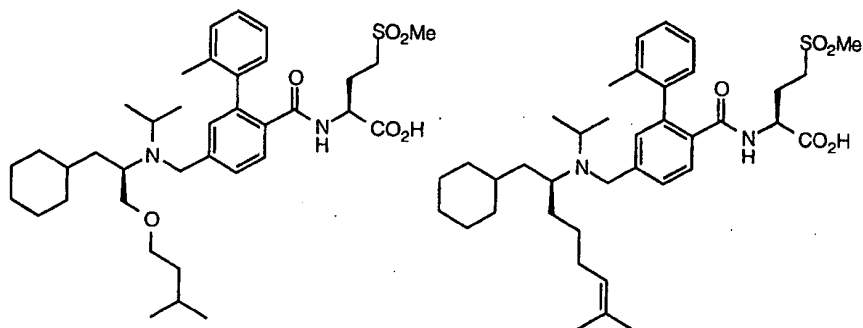


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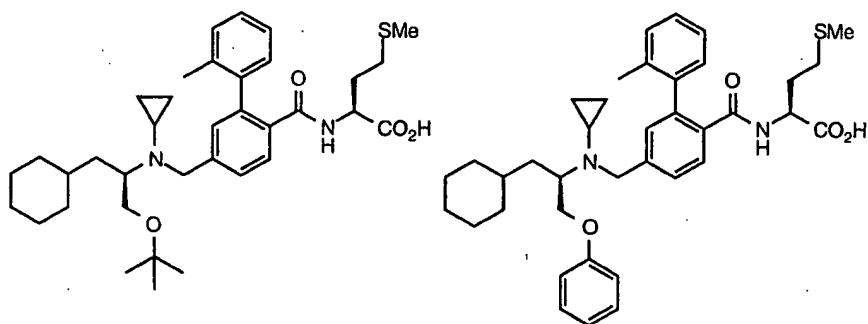


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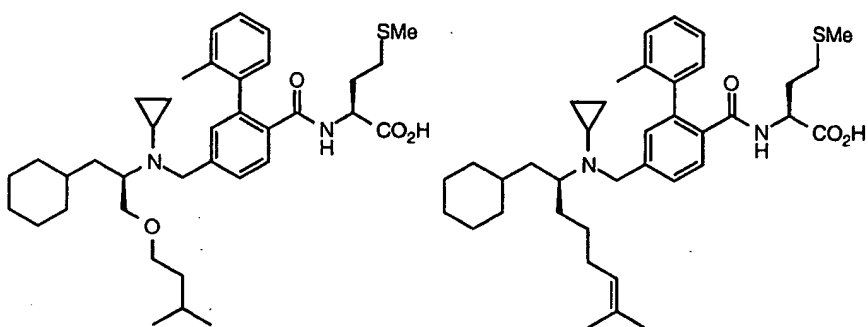


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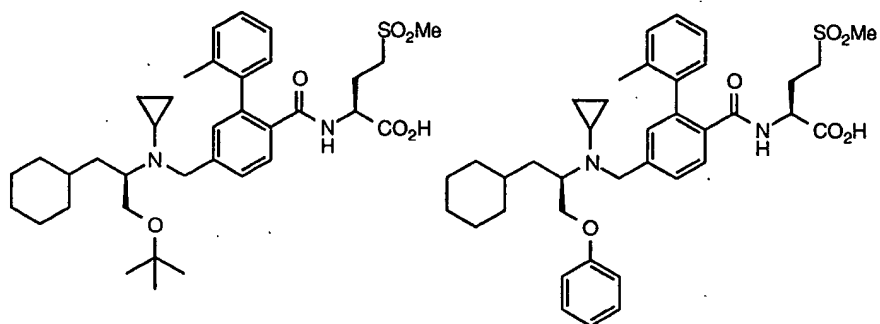
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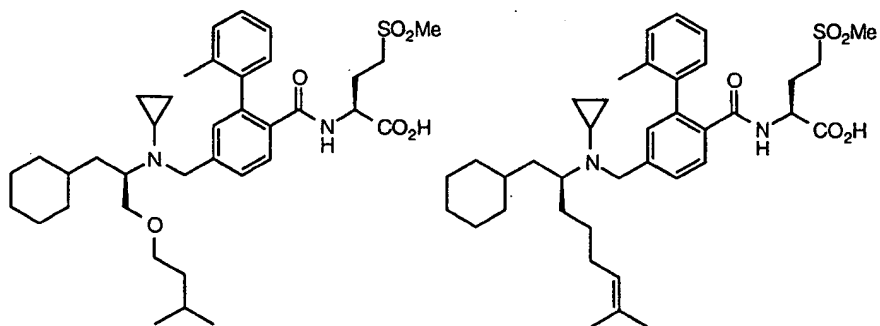
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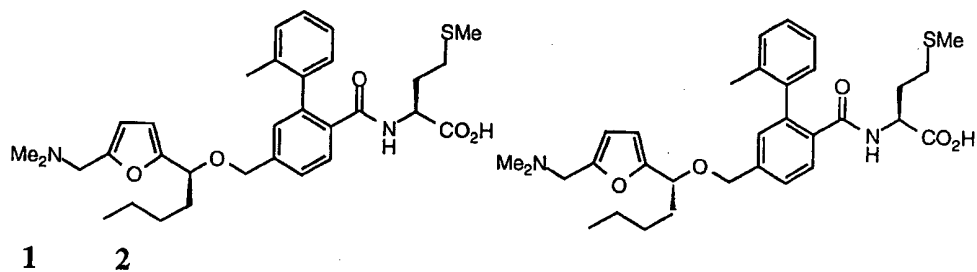
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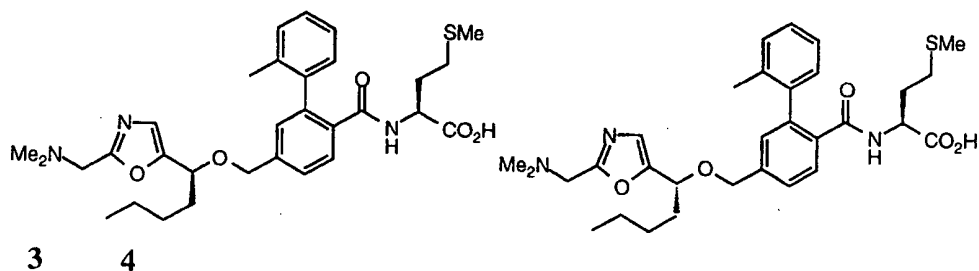
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Table 7. Ethers of the Type A-OL₁

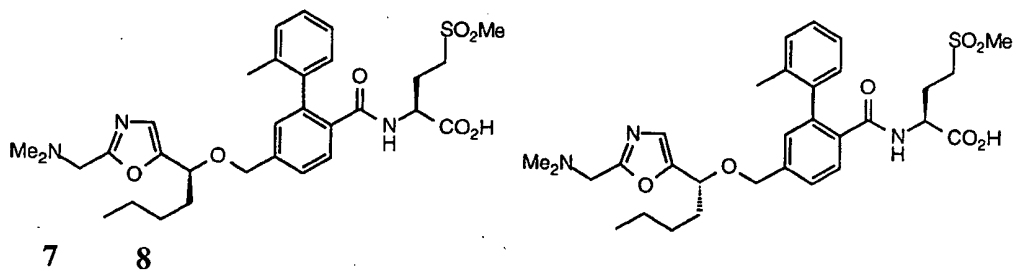
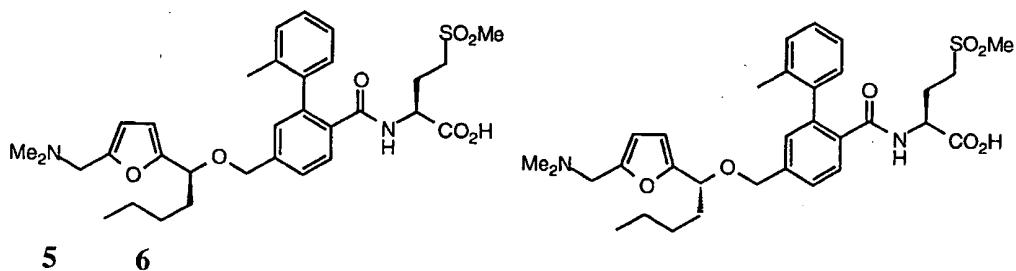
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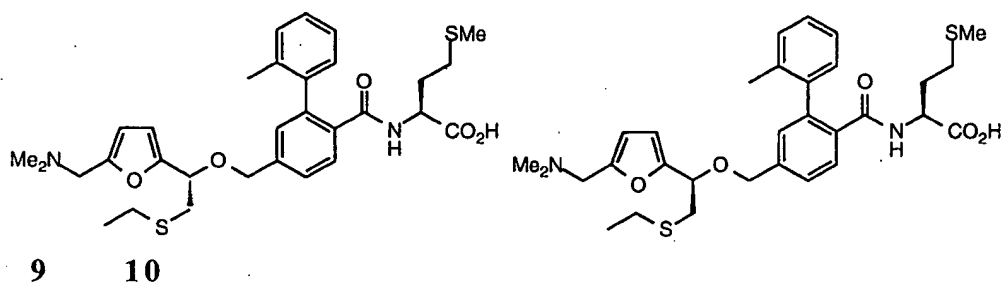
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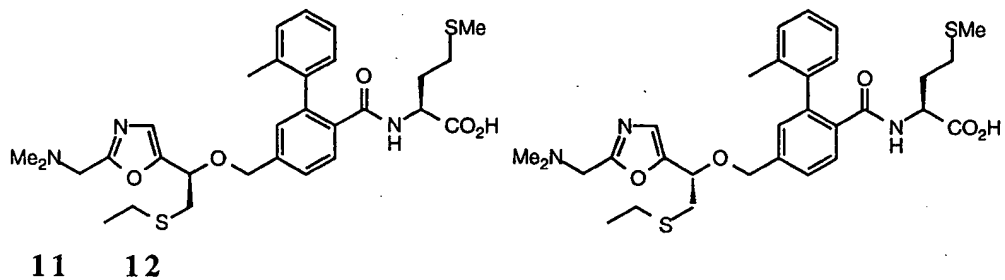
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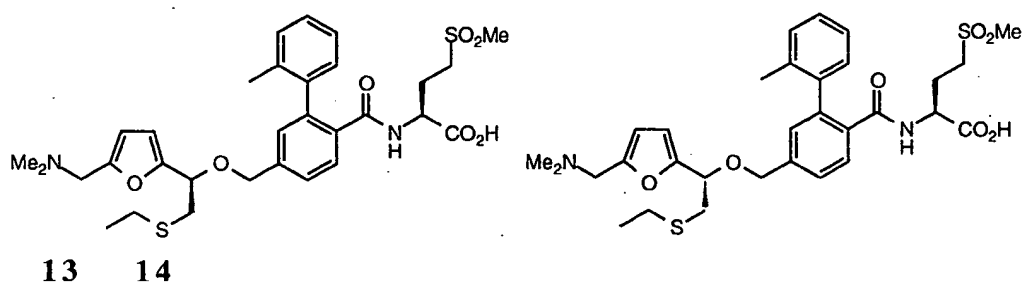
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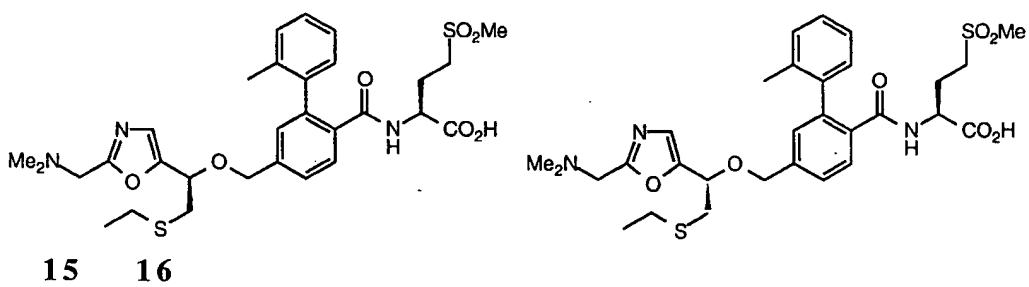
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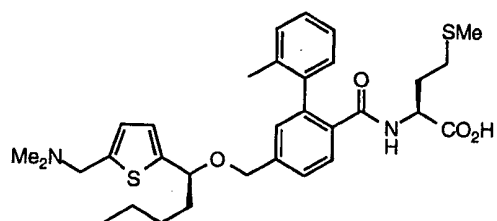
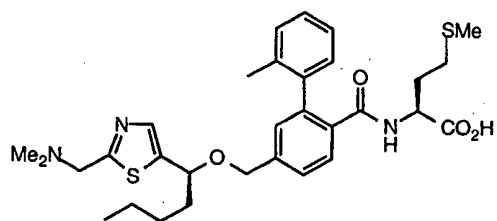
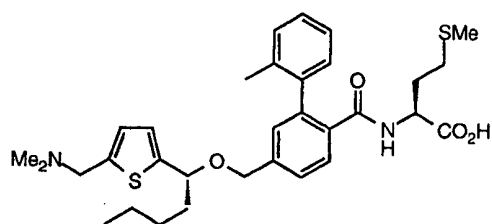
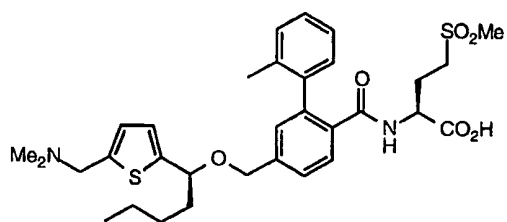
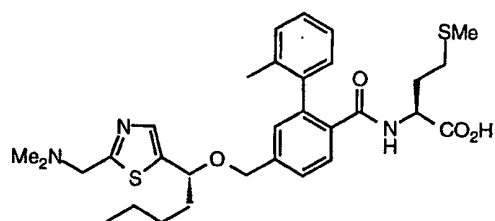
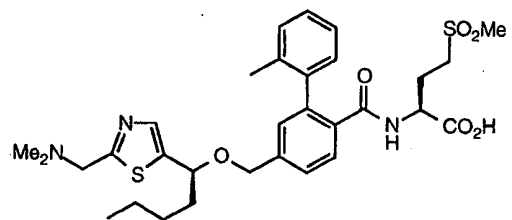
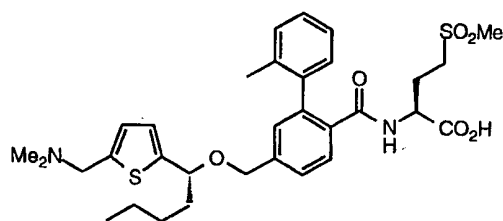
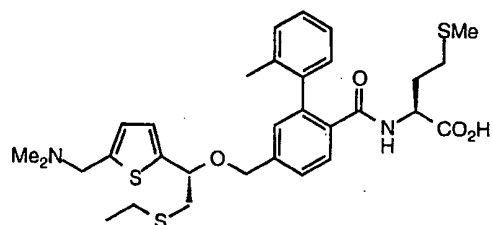
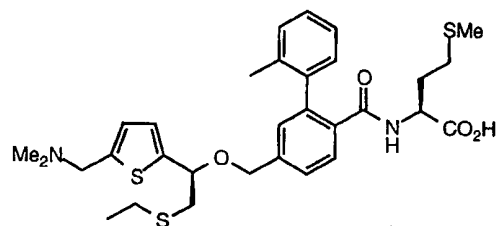
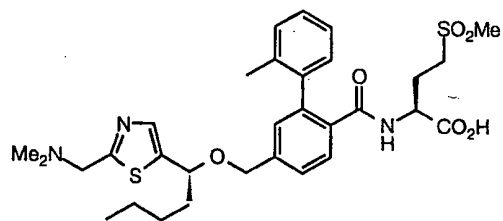


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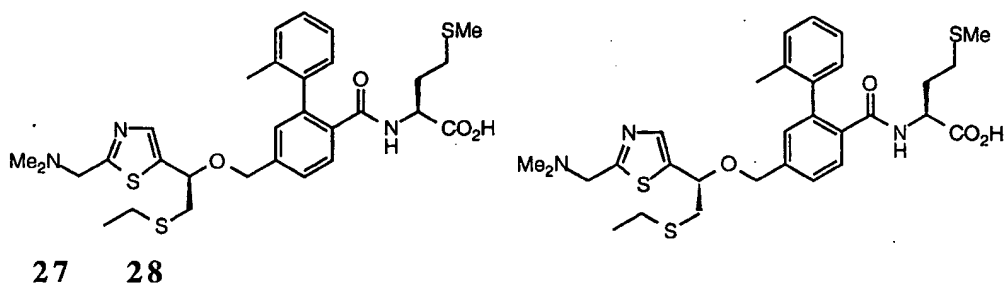
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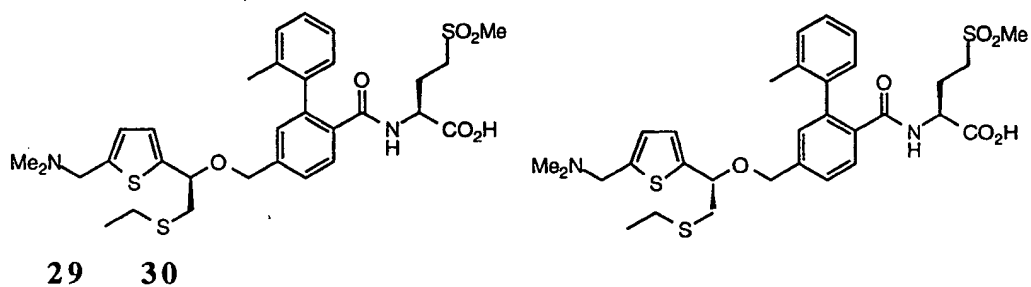
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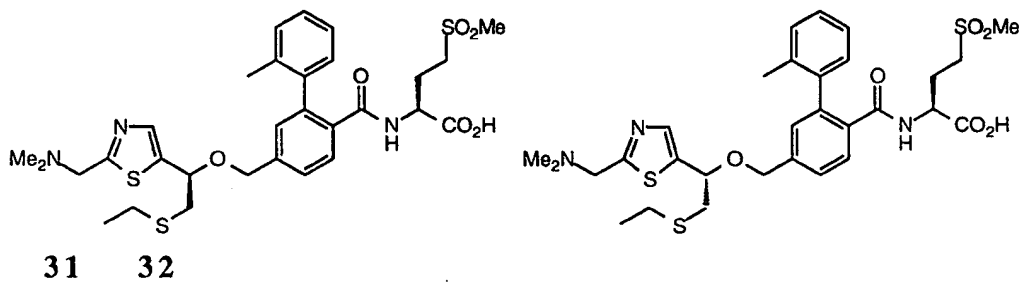
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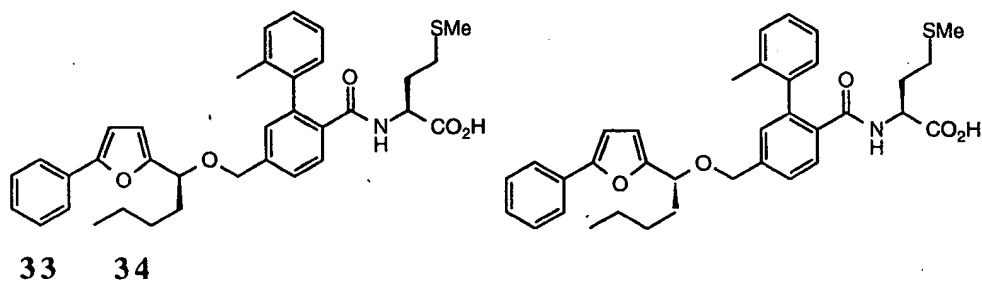
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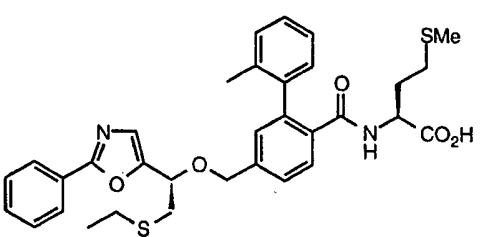
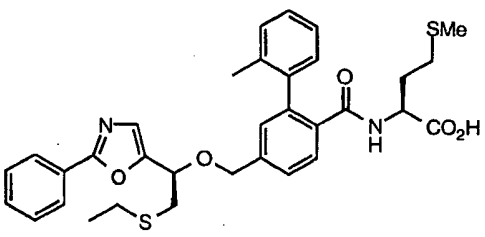
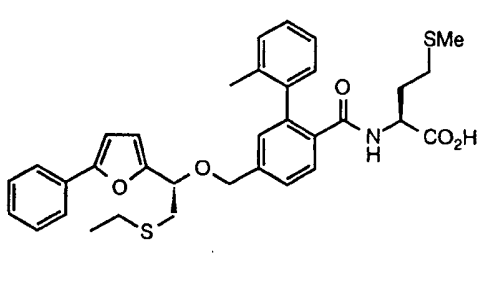
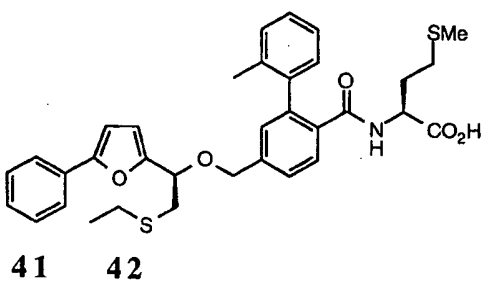
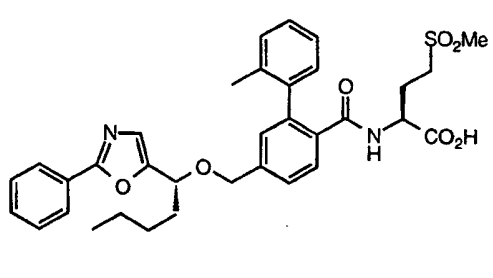
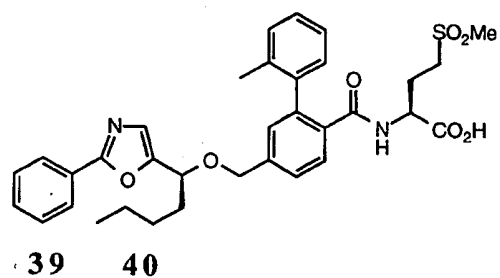
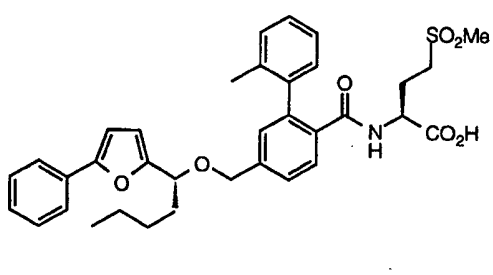
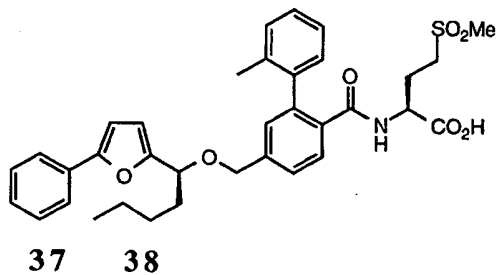
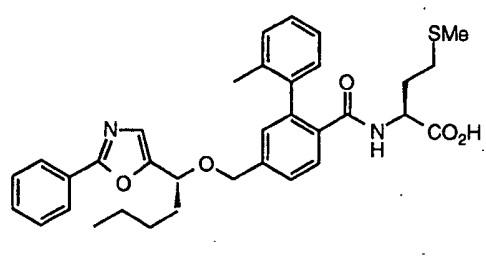
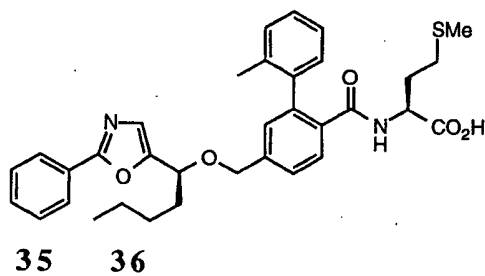


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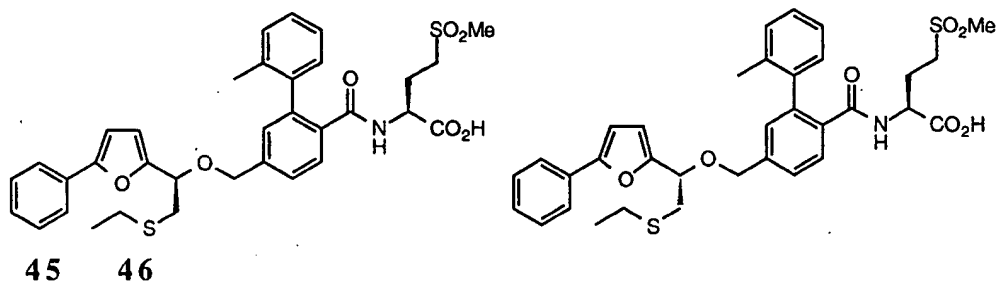
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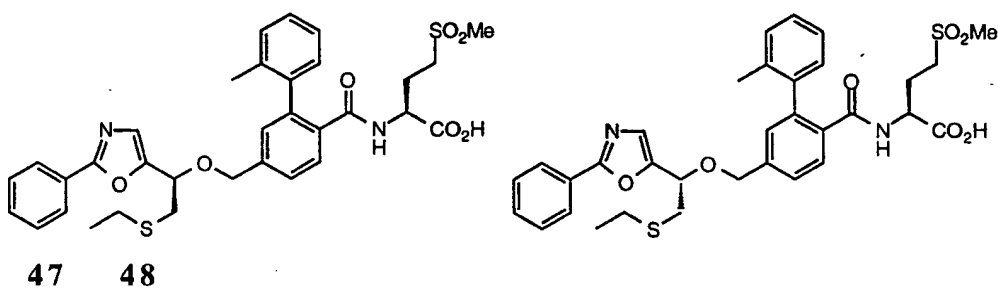


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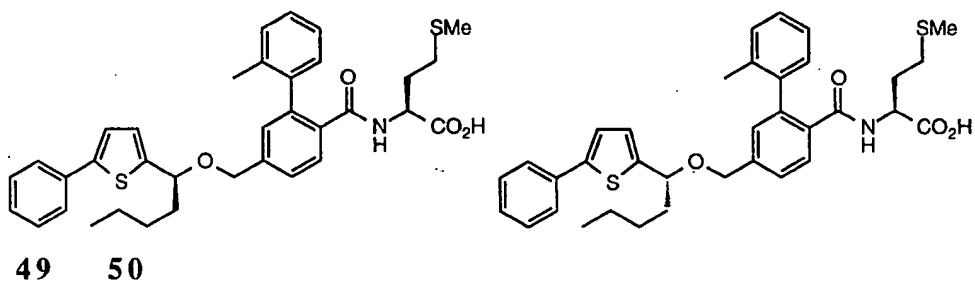
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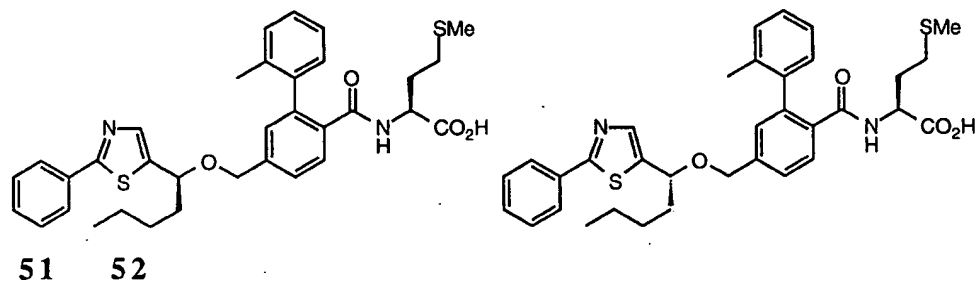
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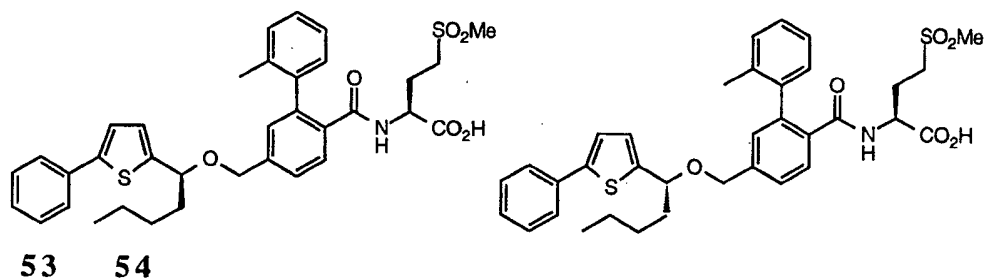


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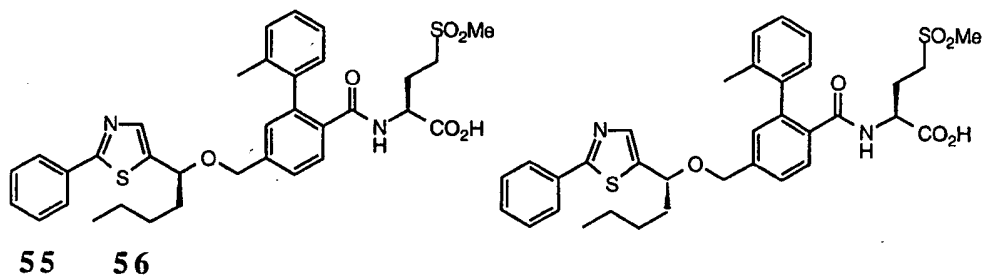


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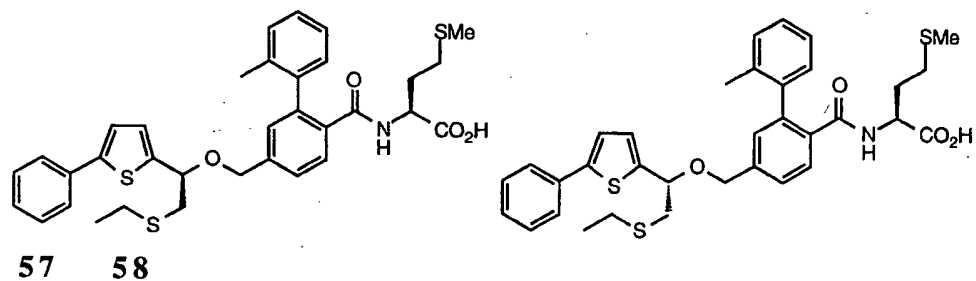




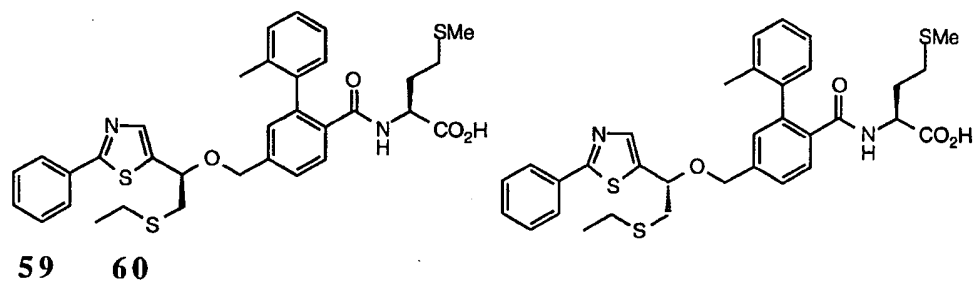
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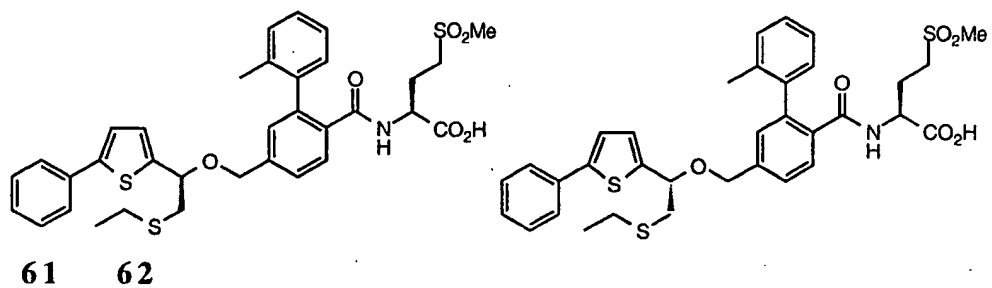


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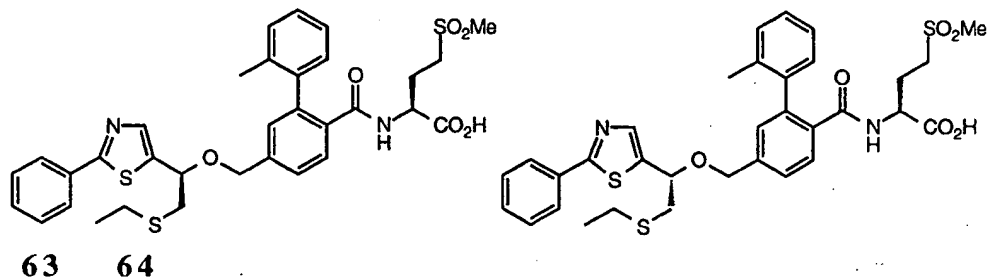


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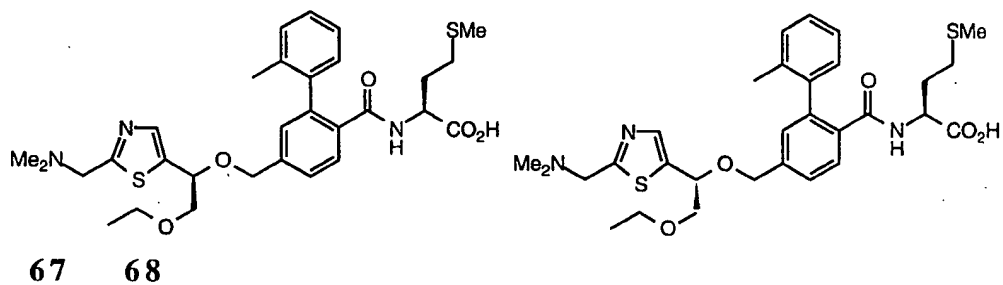
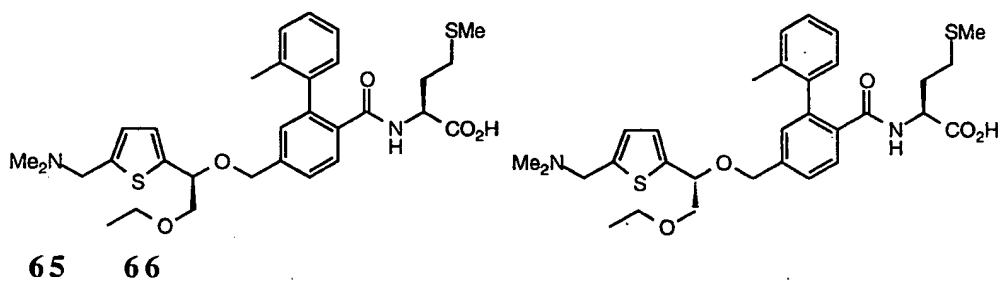




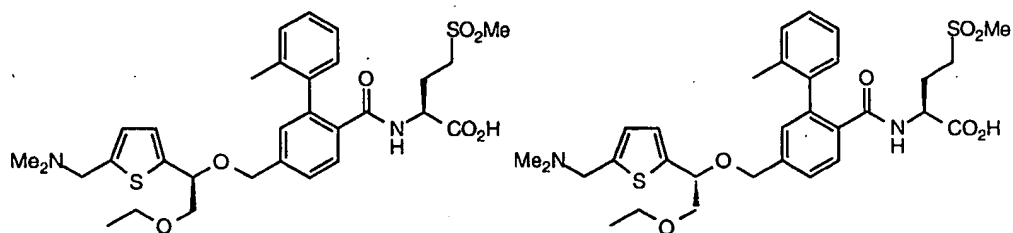
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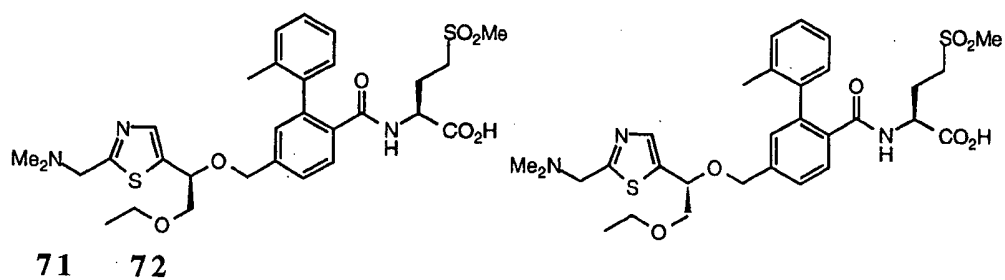


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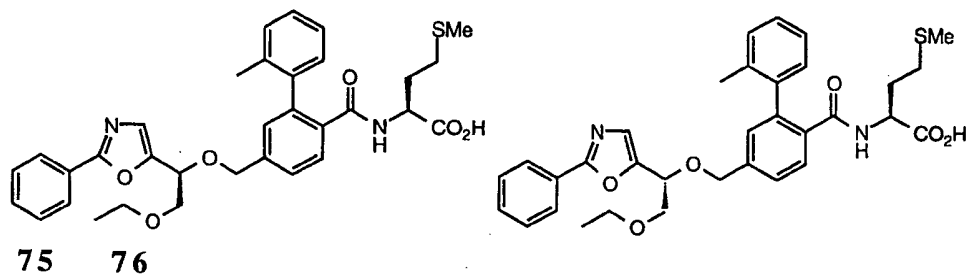
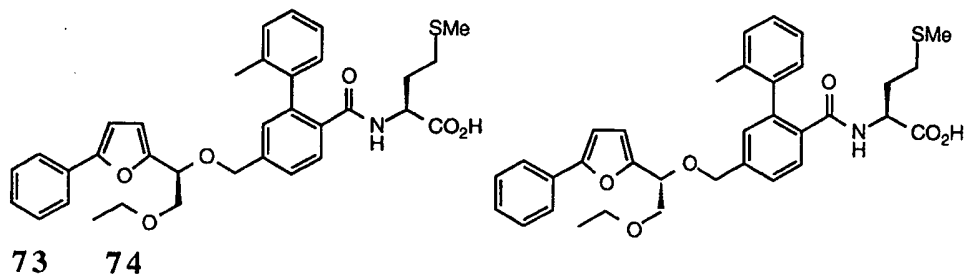


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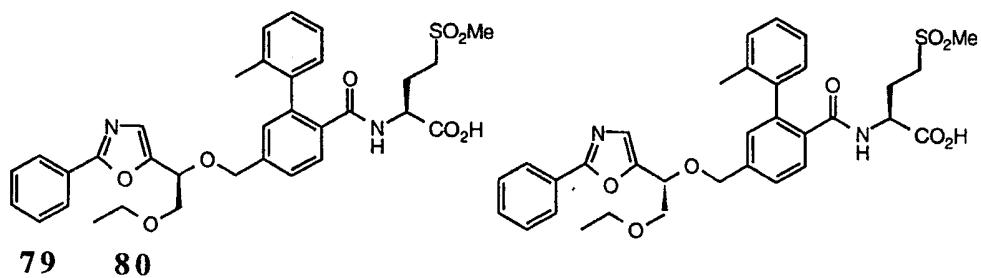
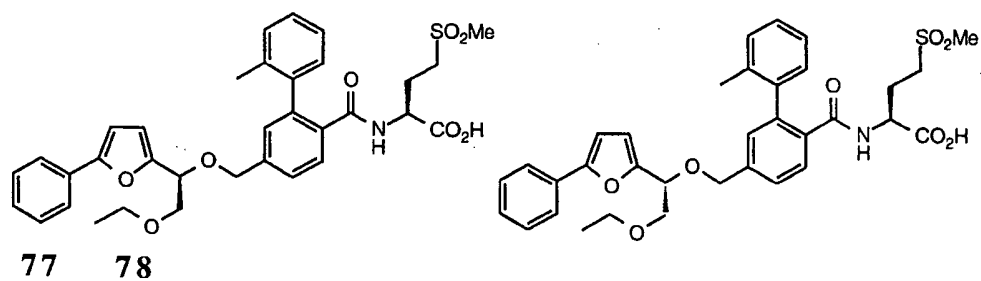
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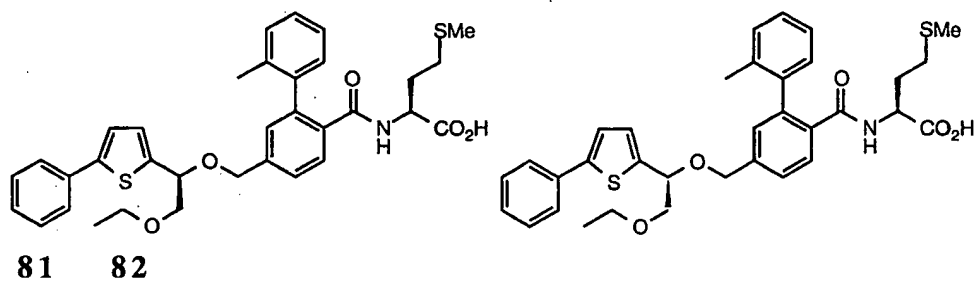
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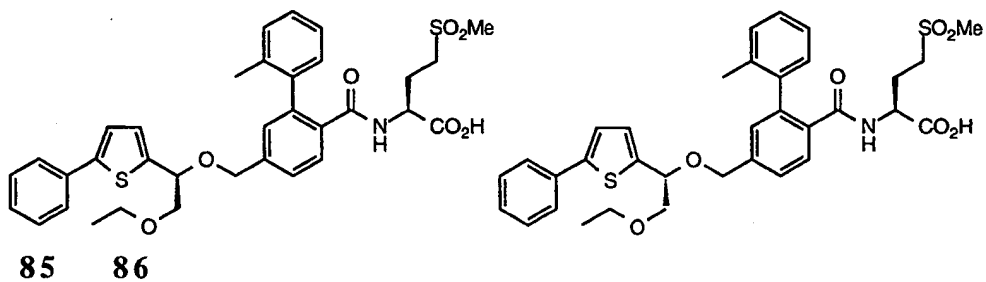
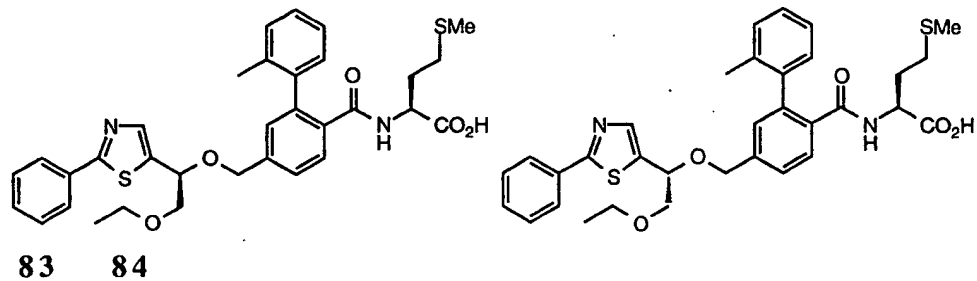
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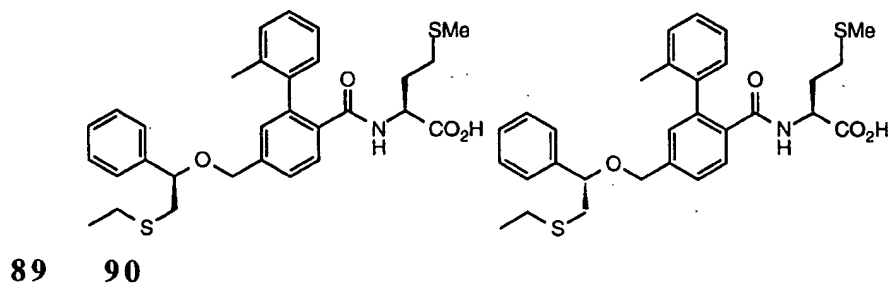
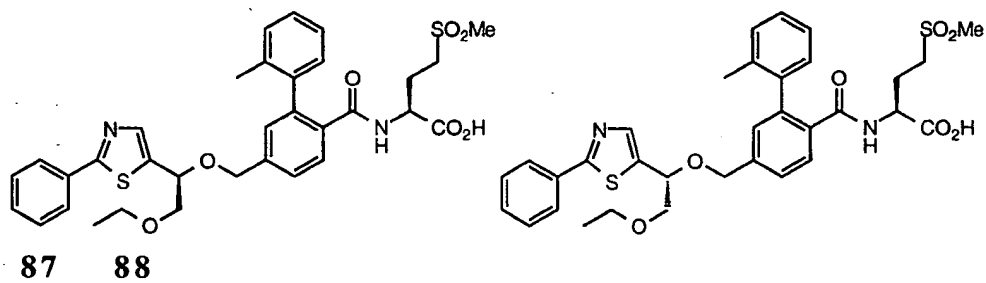
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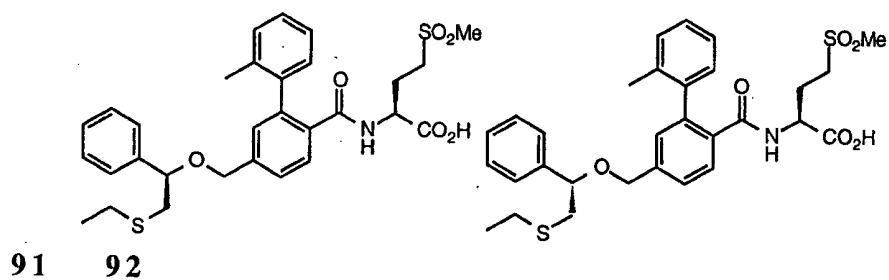
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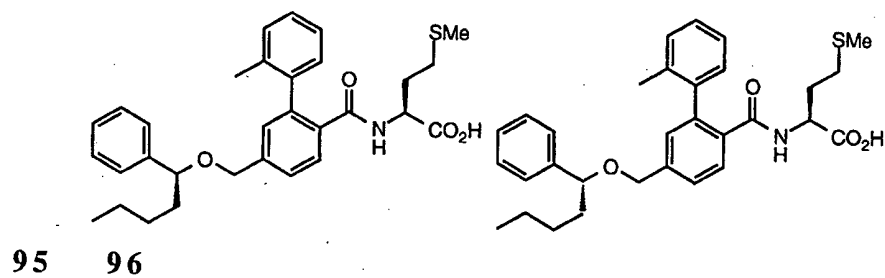
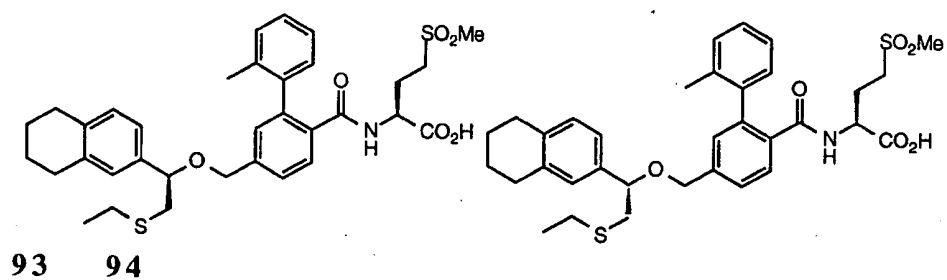
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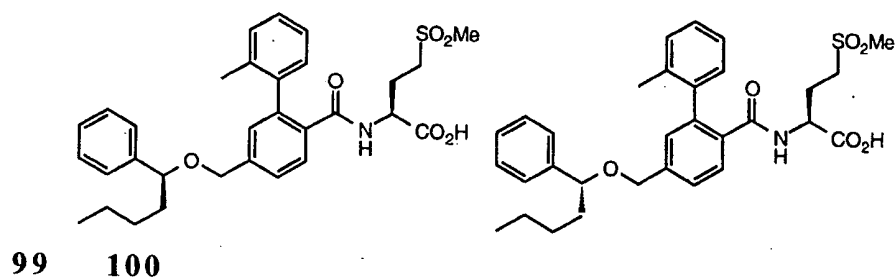
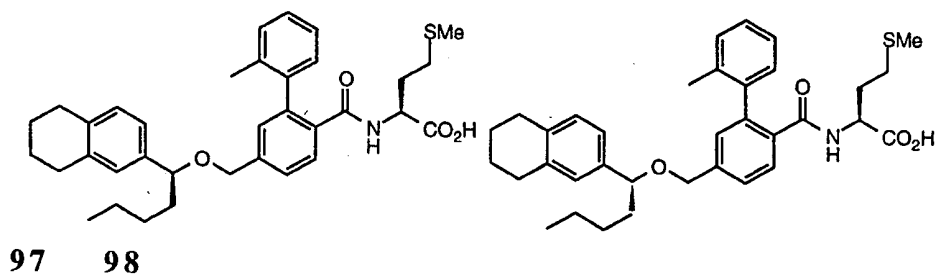
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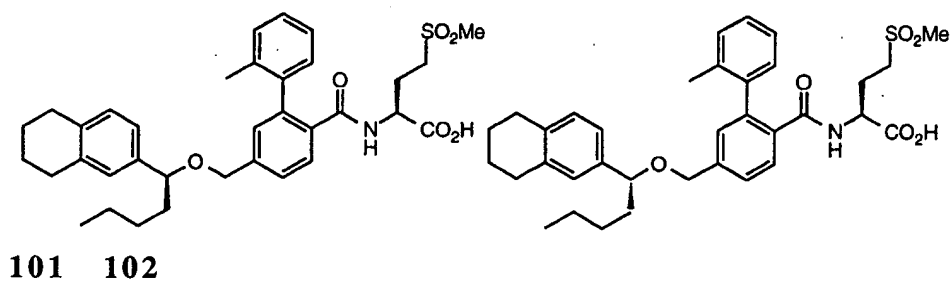
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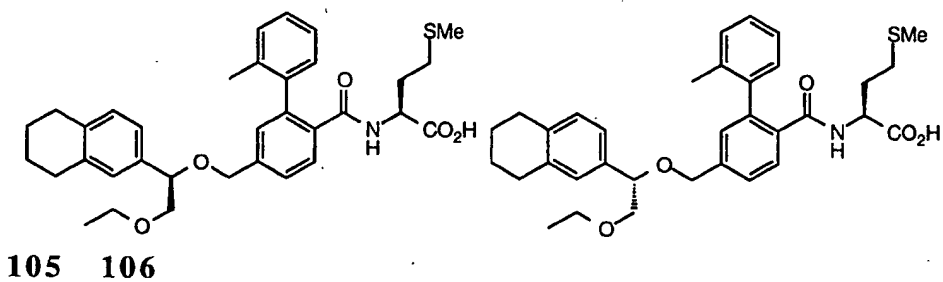
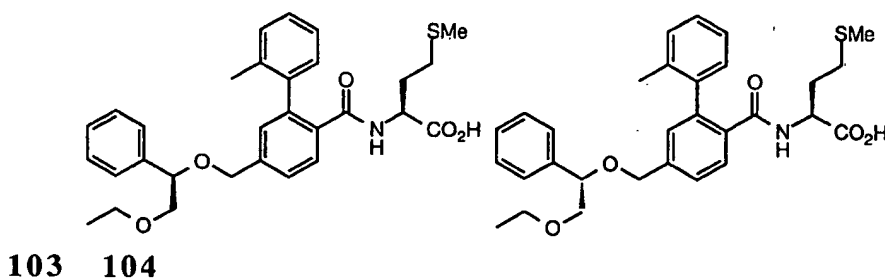
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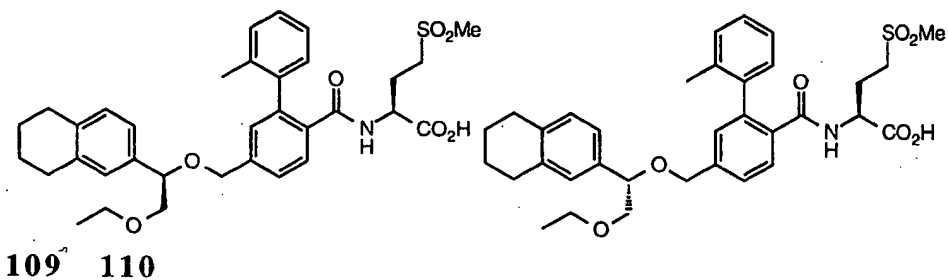
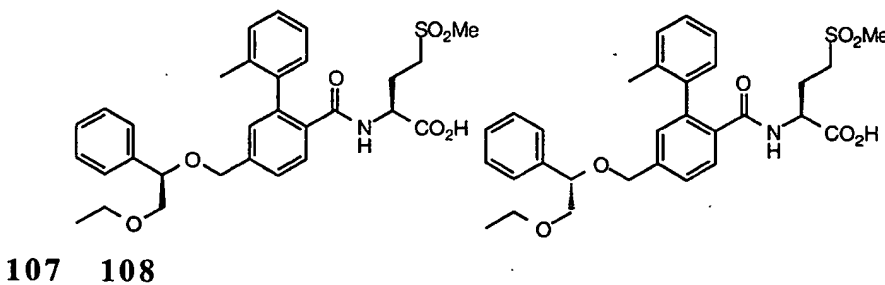
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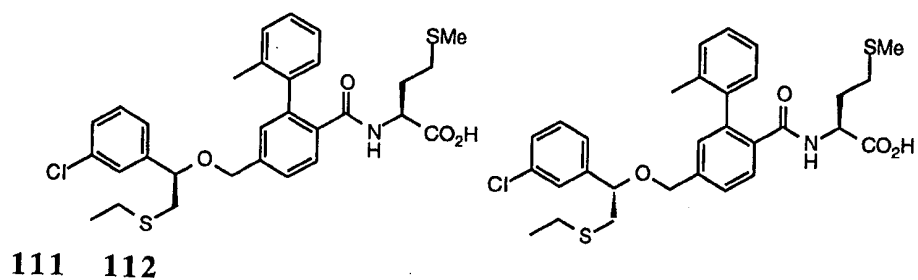
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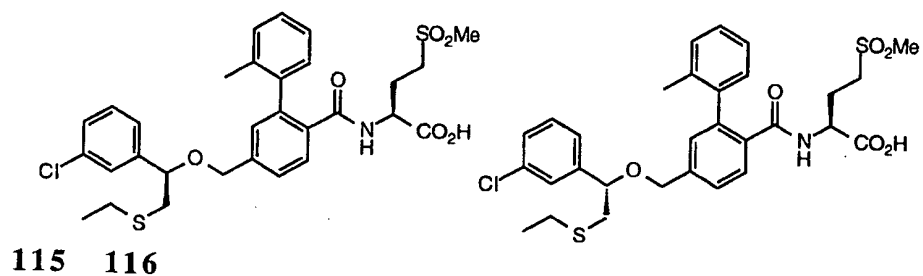
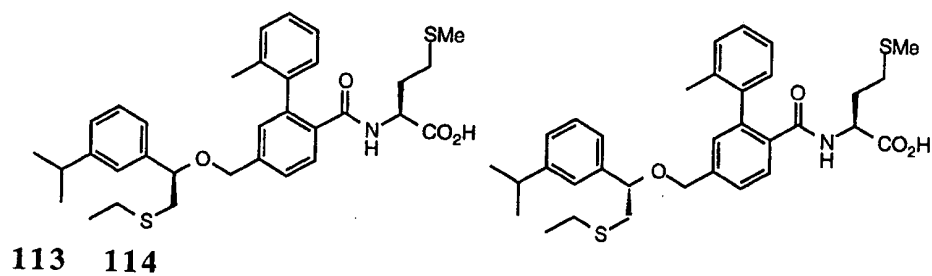
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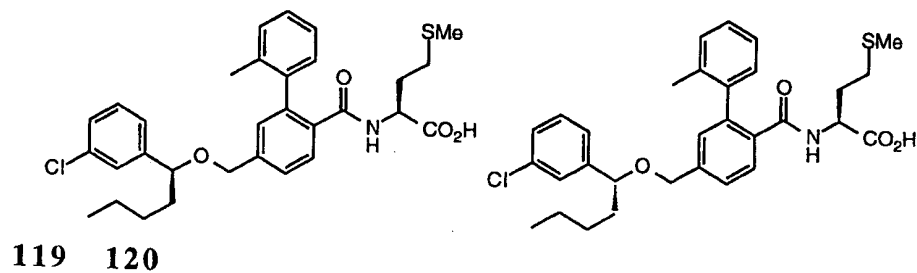
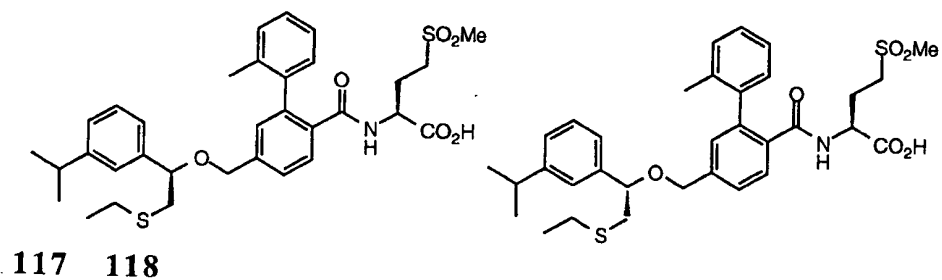
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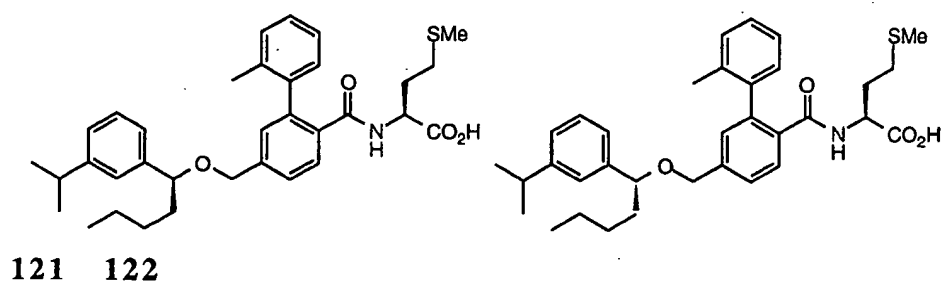
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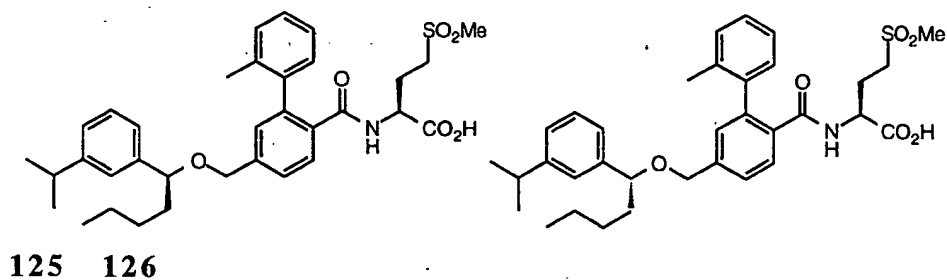
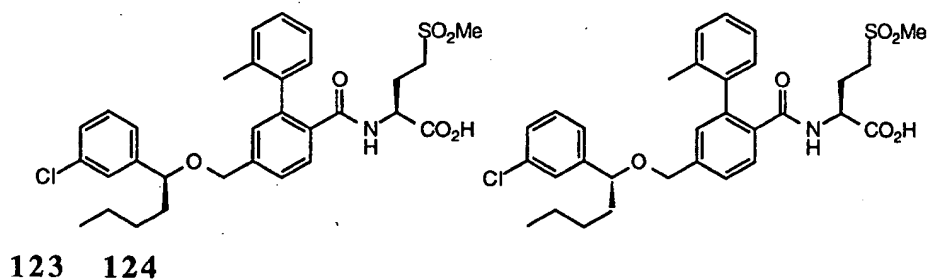
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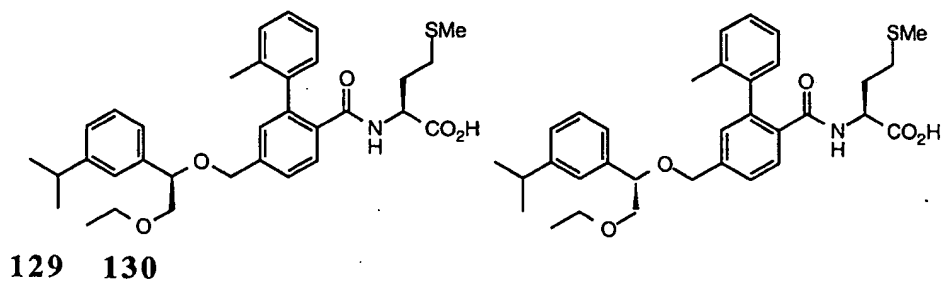
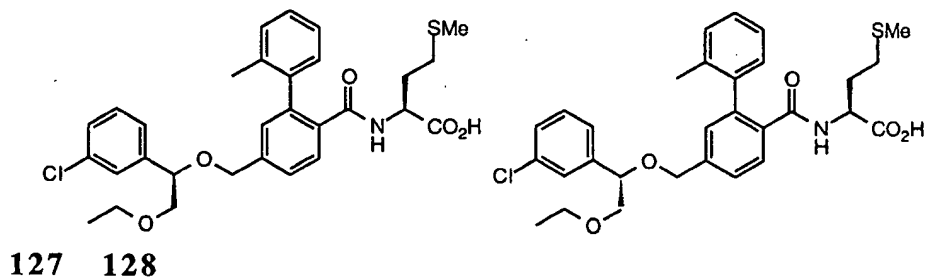
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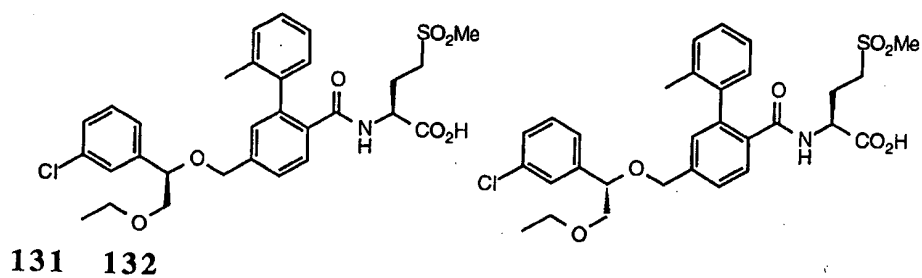
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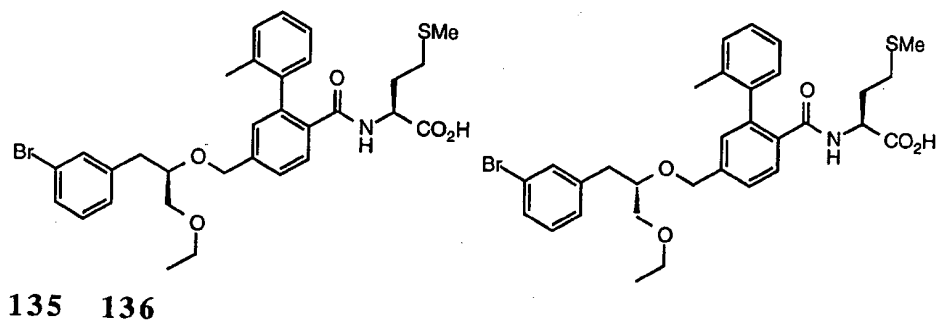
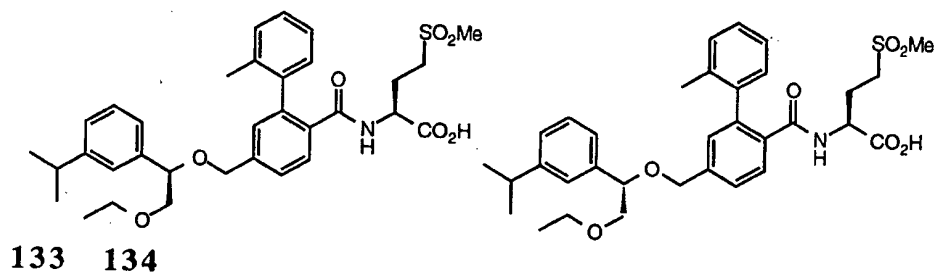
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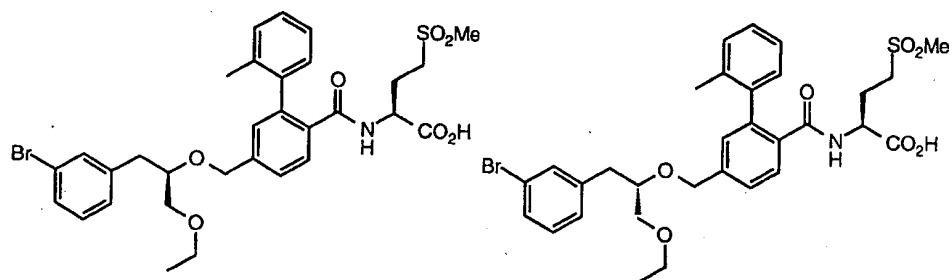
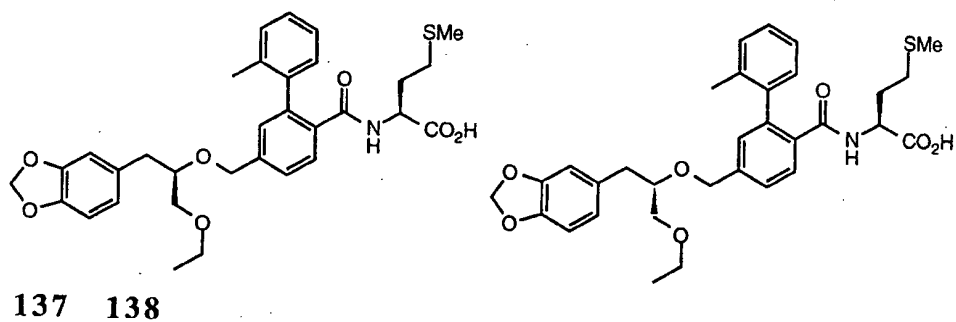
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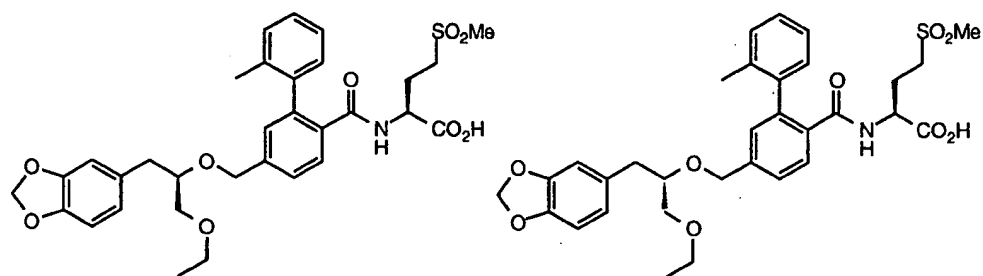
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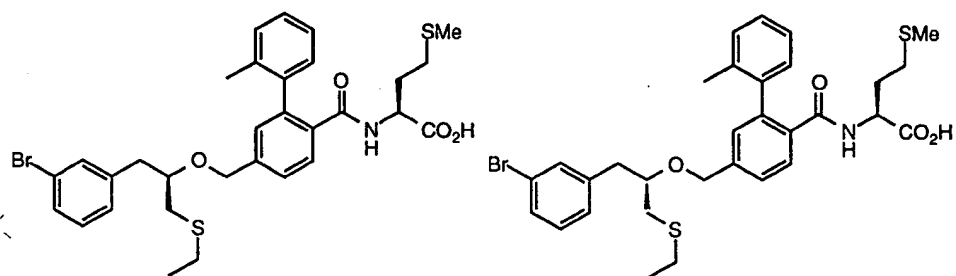


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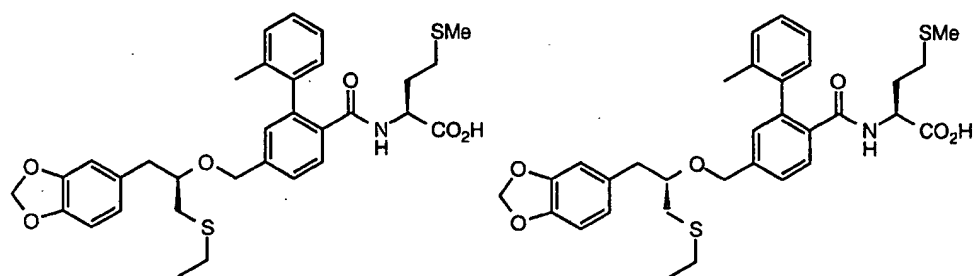


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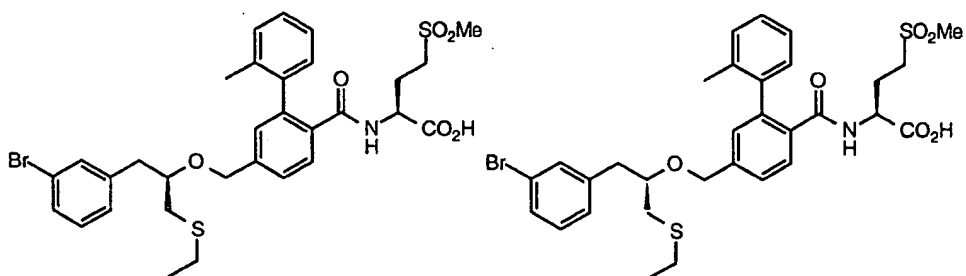


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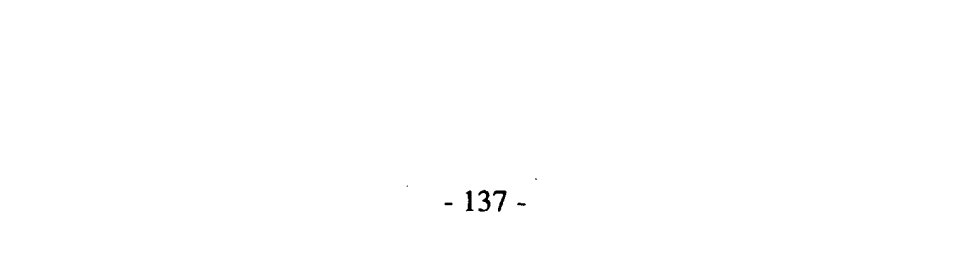
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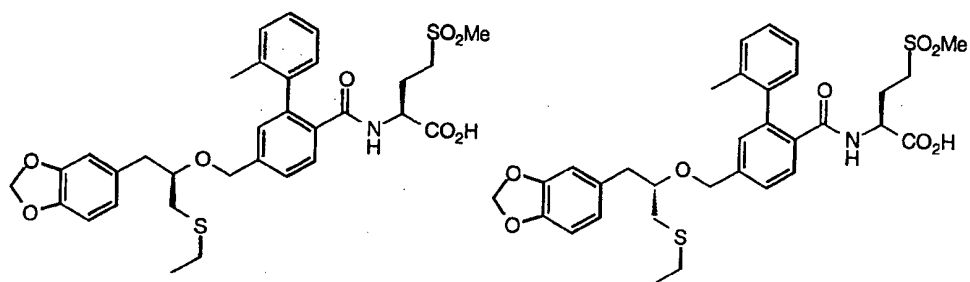
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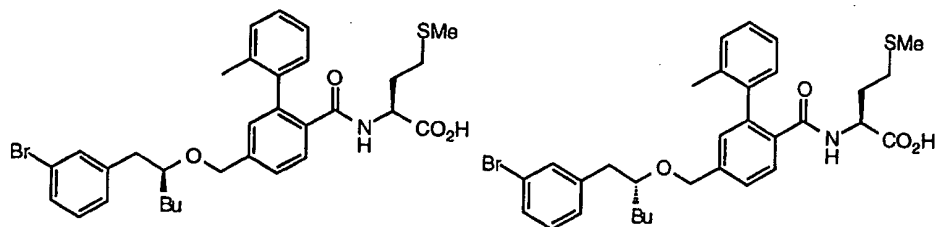
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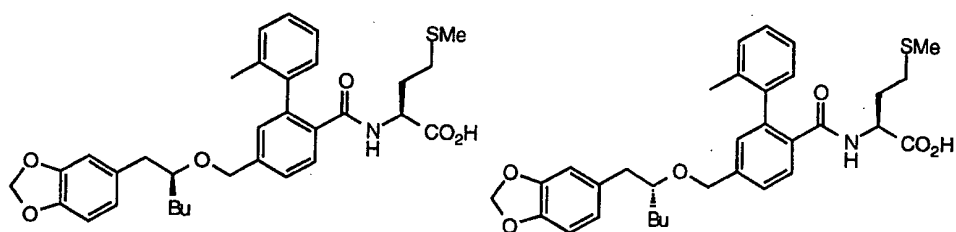


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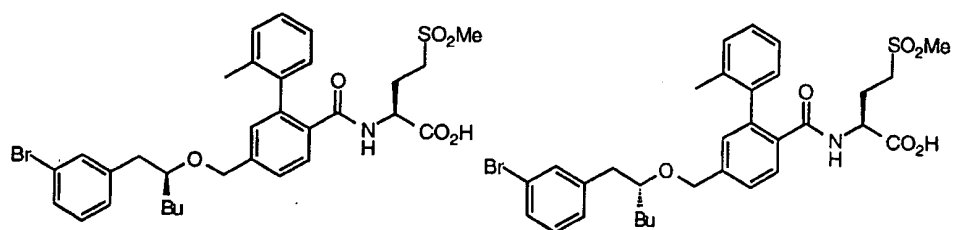
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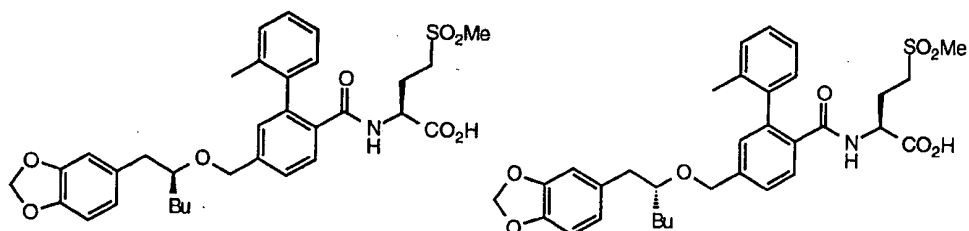


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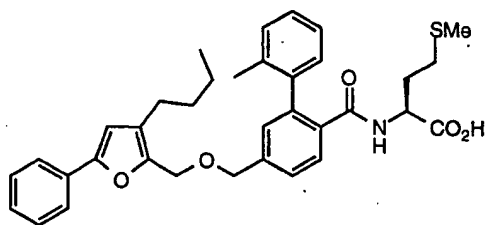
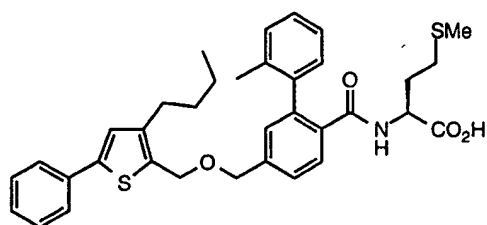


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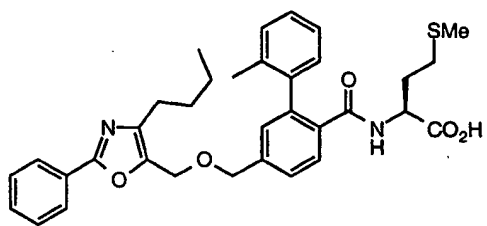
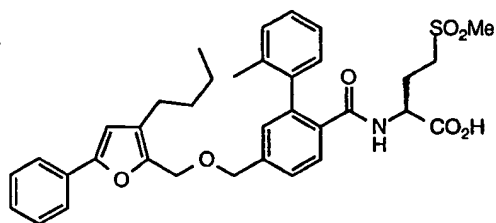
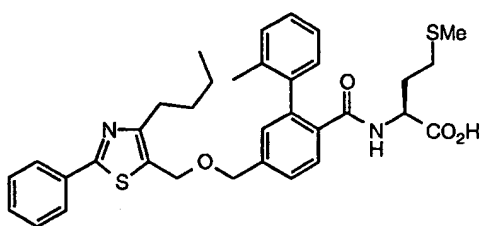
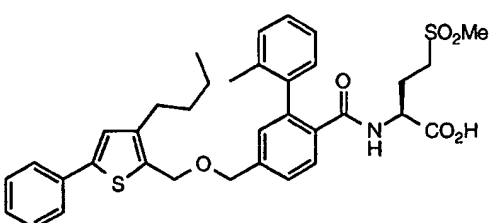


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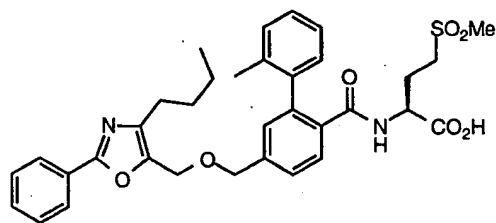
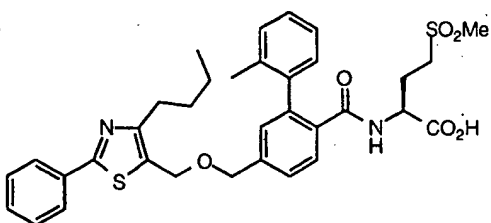
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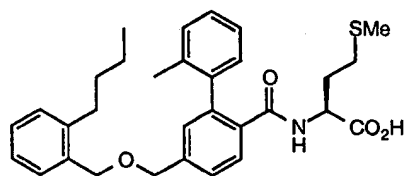
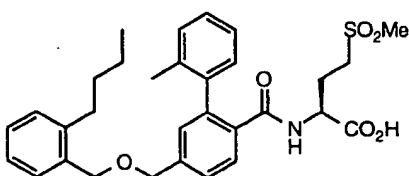
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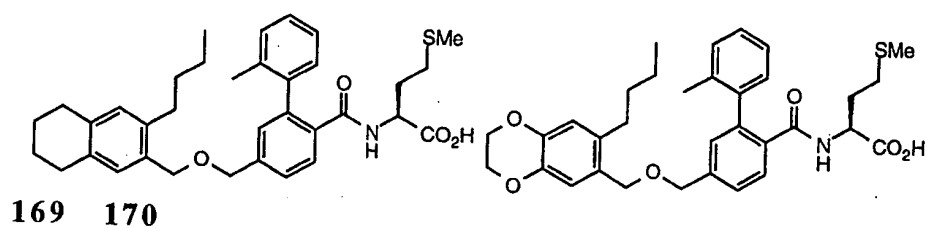
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2345

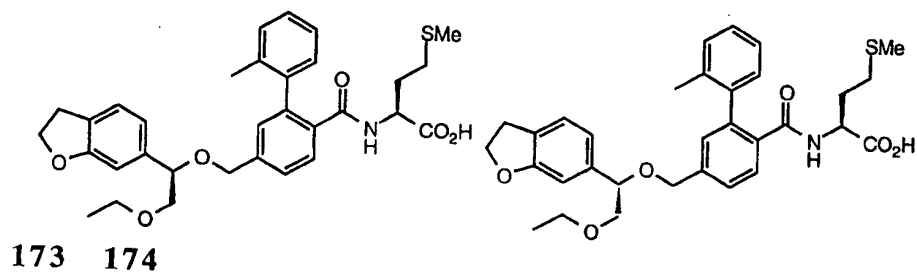
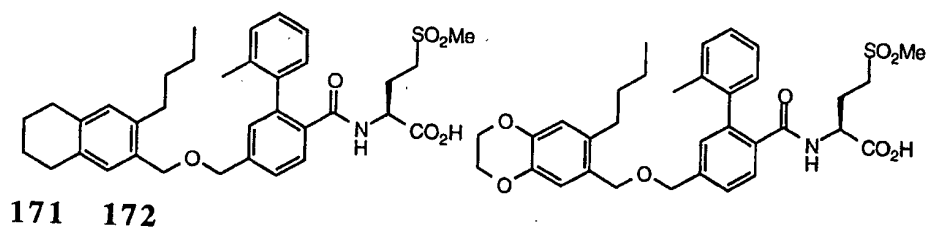
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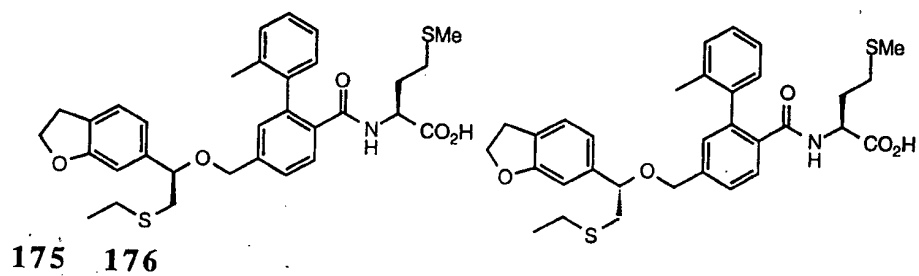
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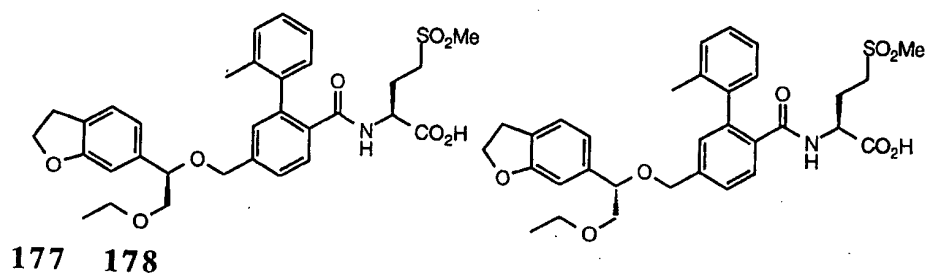
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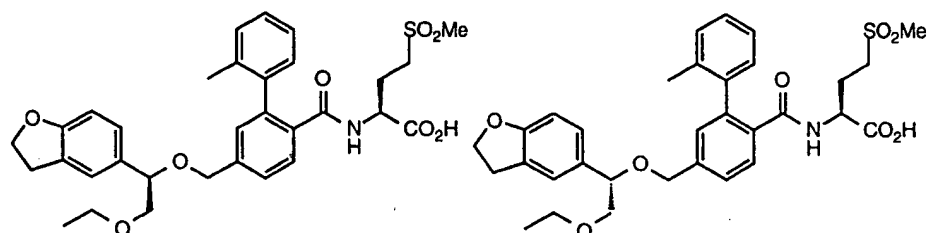
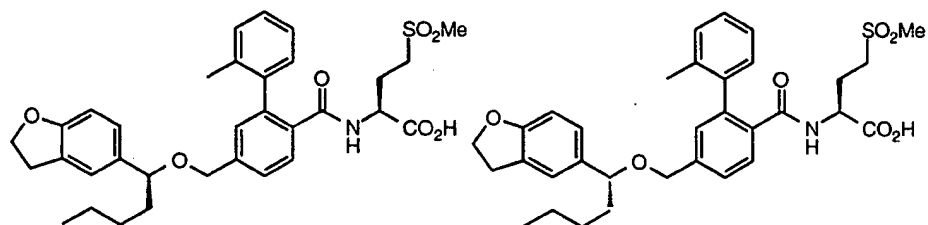
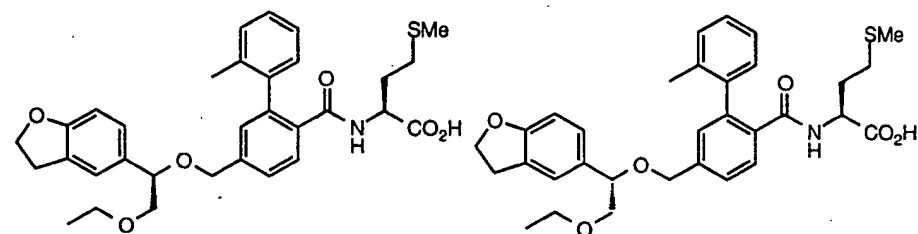
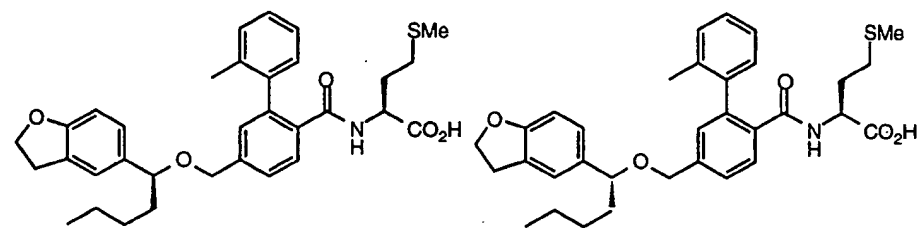
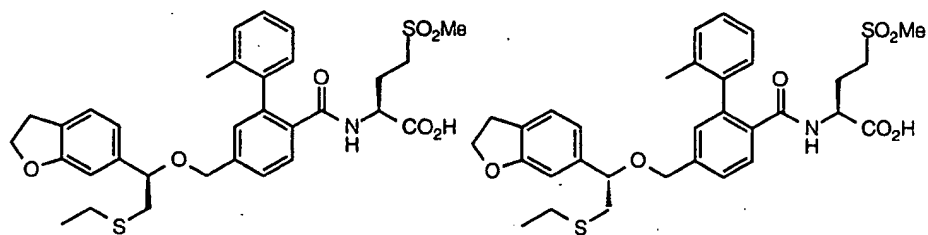


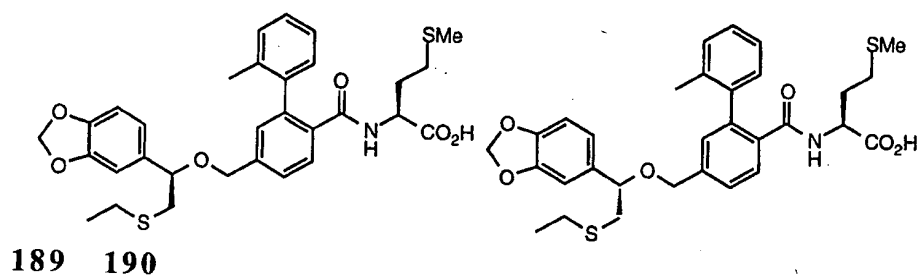
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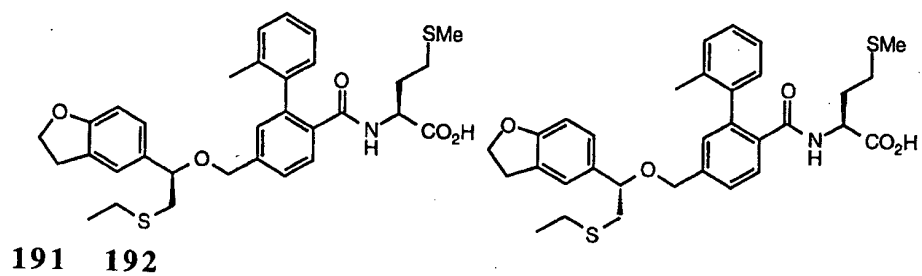
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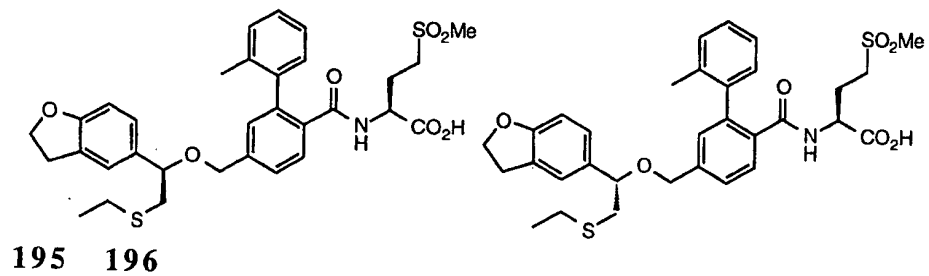
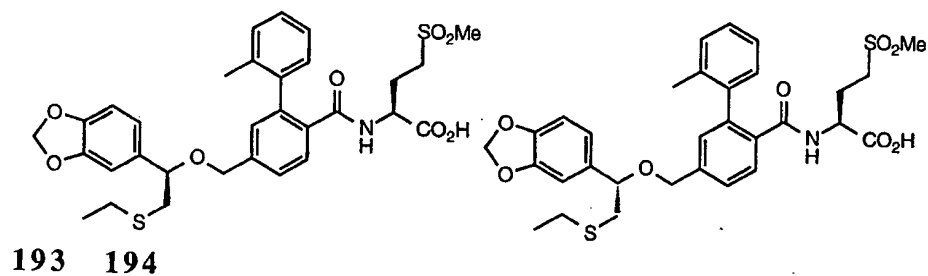




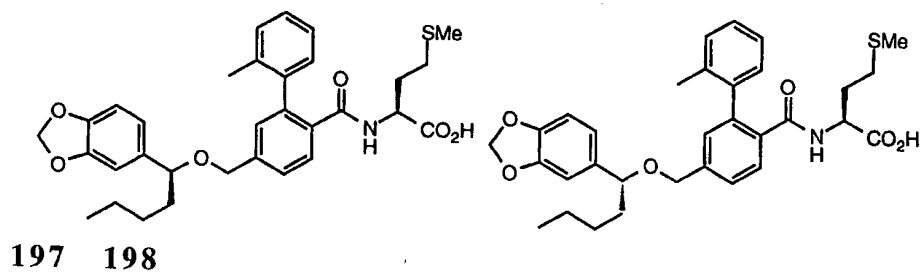
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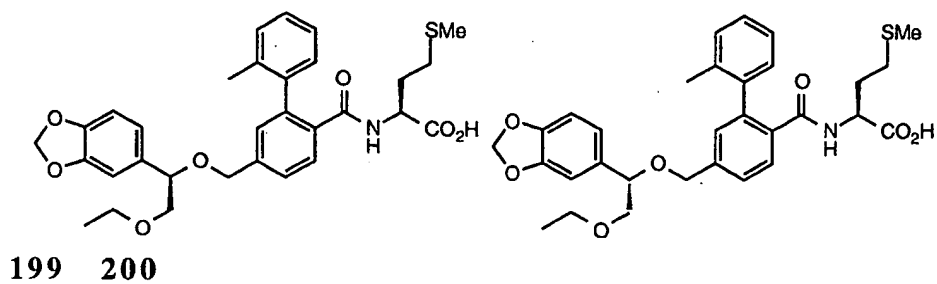


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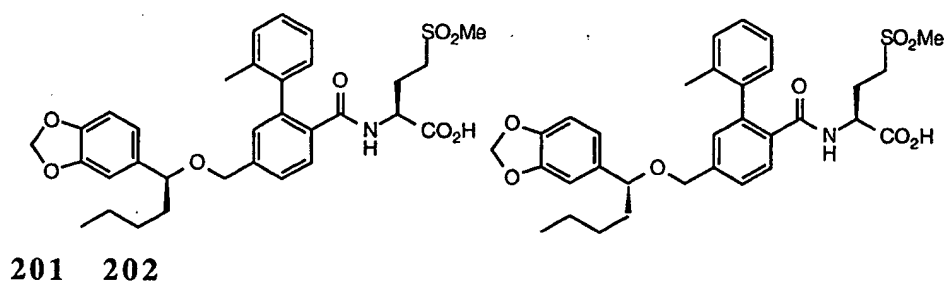


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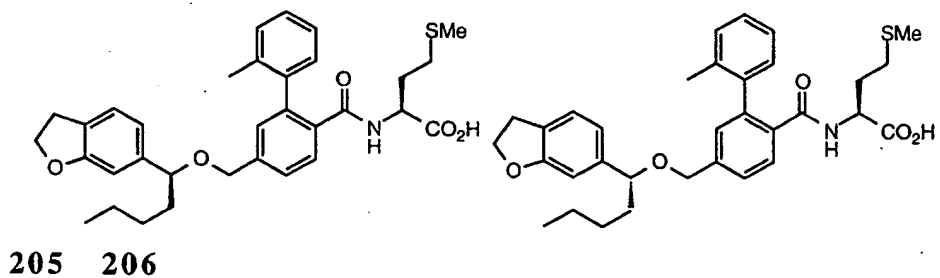
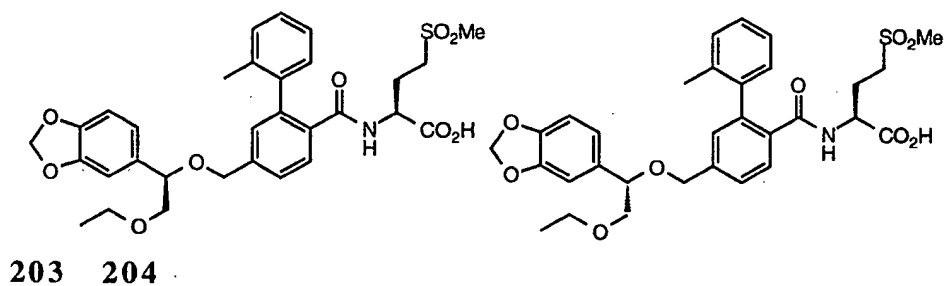




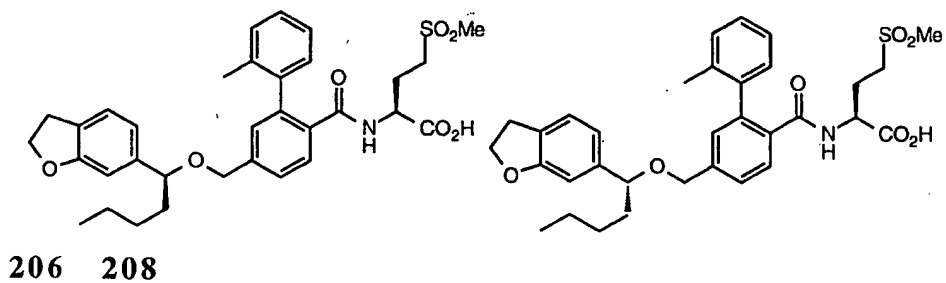
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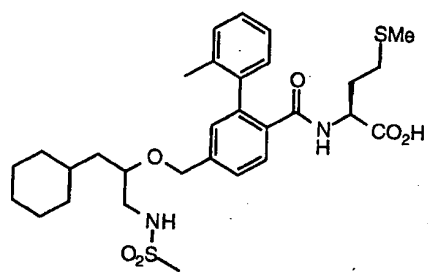


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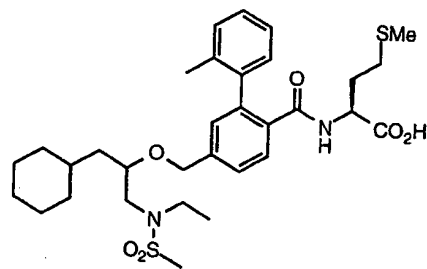
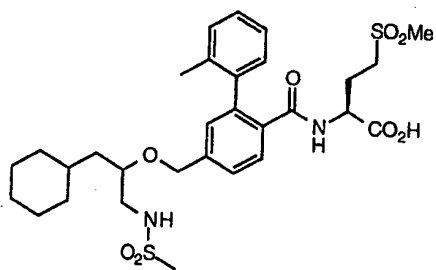


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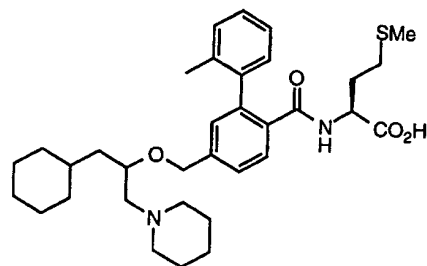
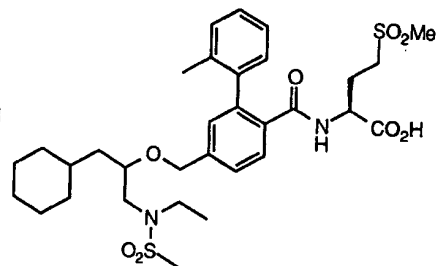




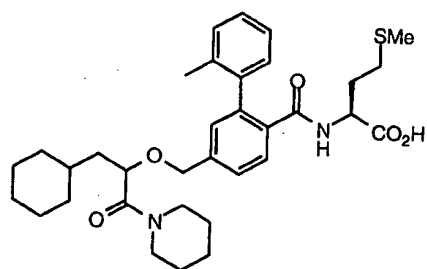
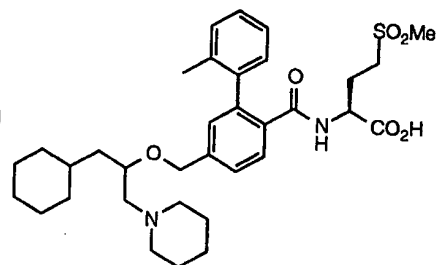
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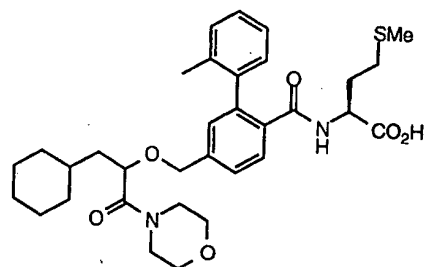
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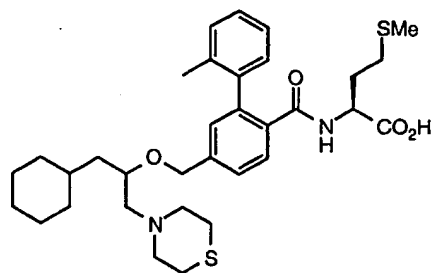
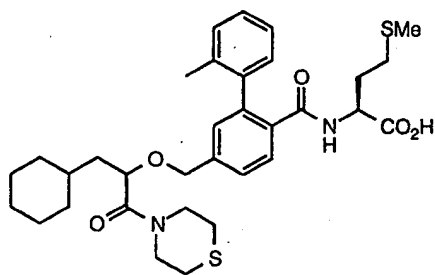


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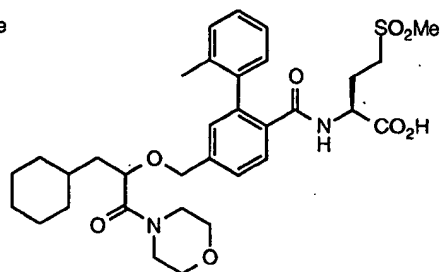
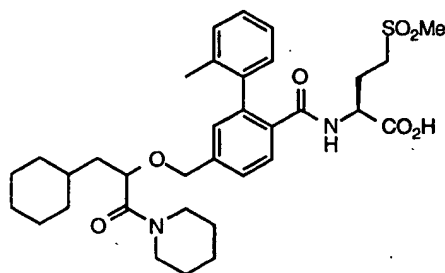
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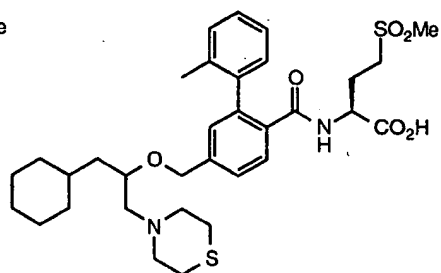
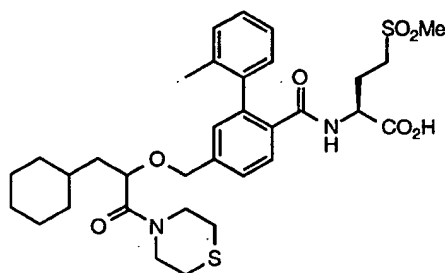


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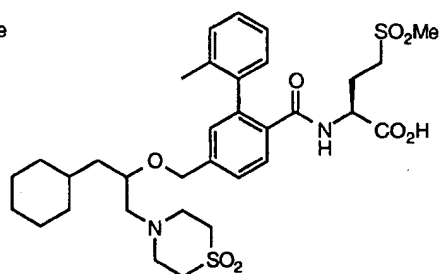
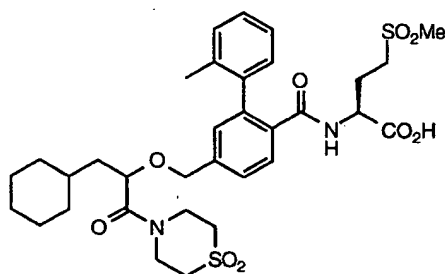


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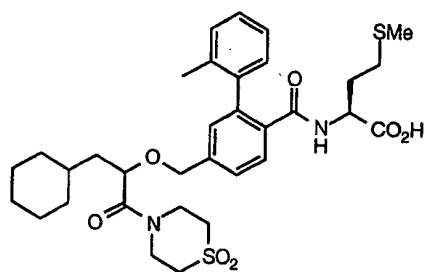
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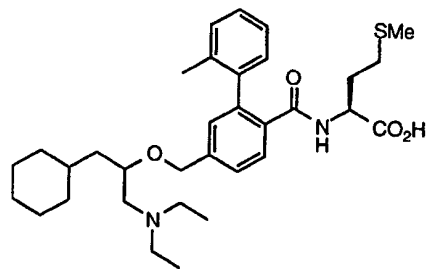
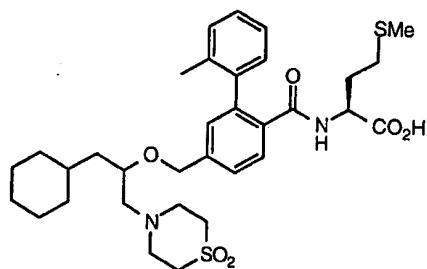


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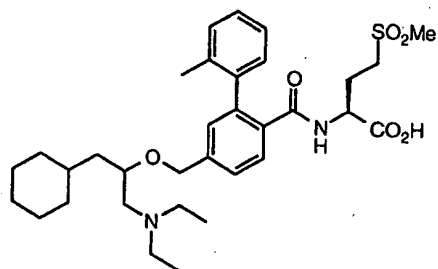
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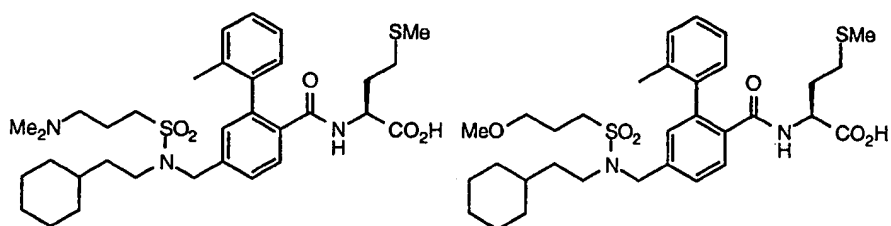
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227 228

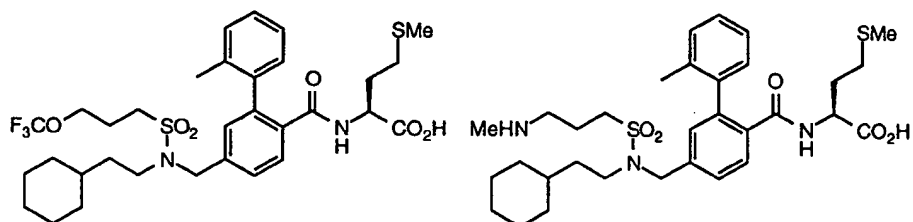


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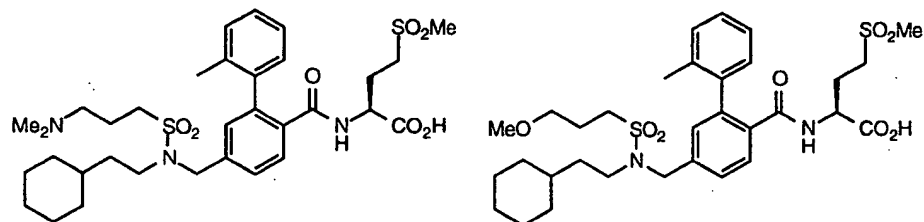
Table 8. Sulfonamides of the Type $\text{ASO}_2(\text{B})\text{N-L}_1$ 

2445

1 2

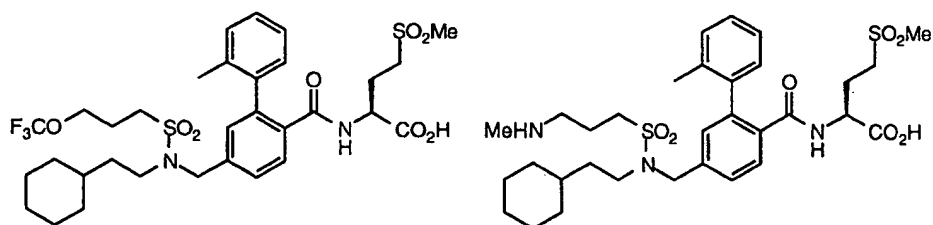


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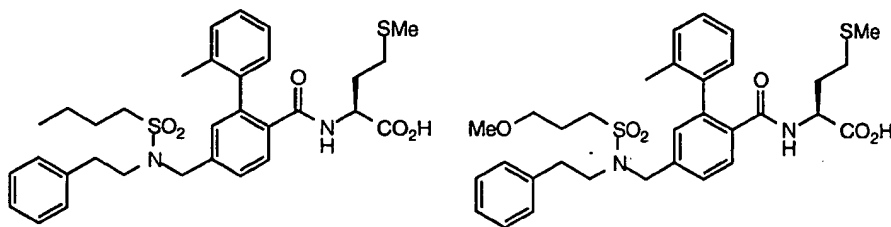
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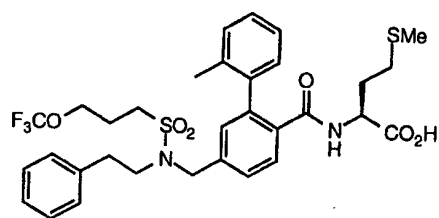


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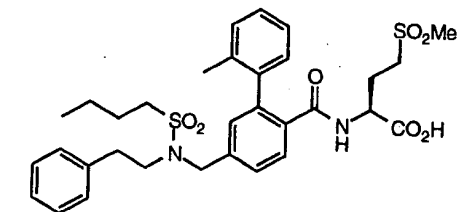
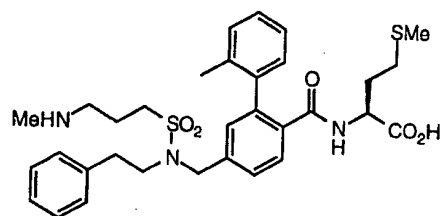


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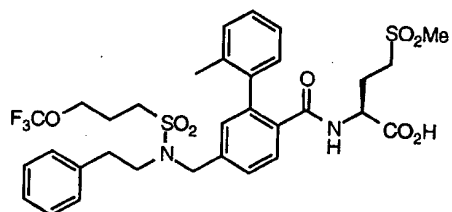
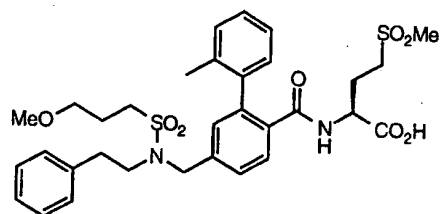


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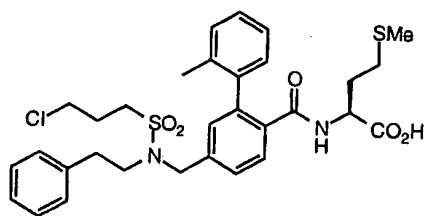
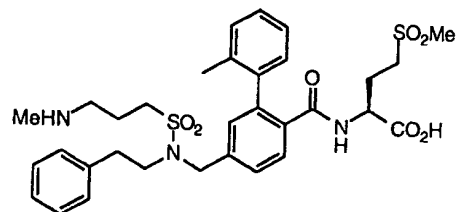


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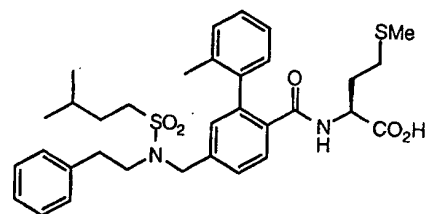


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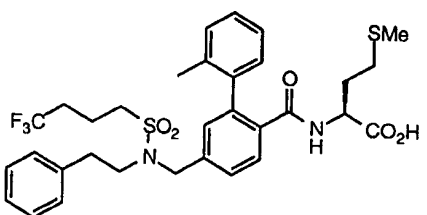
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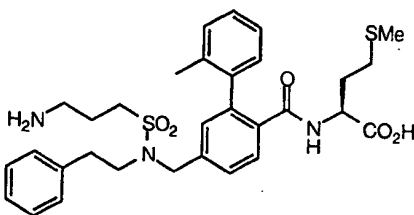
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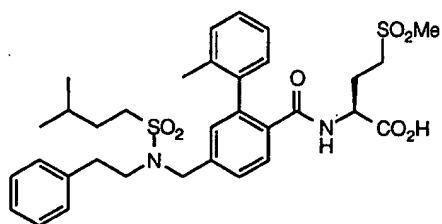
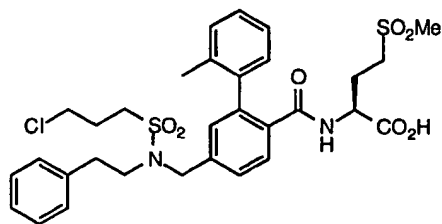


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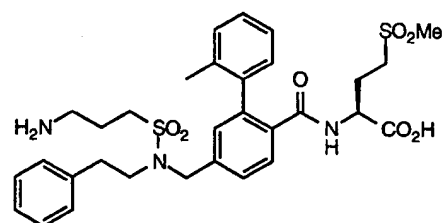
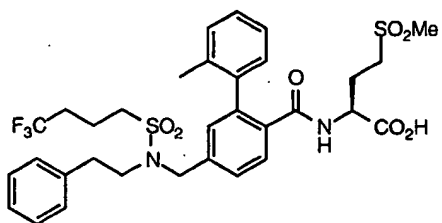
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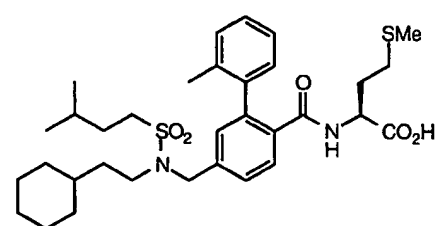
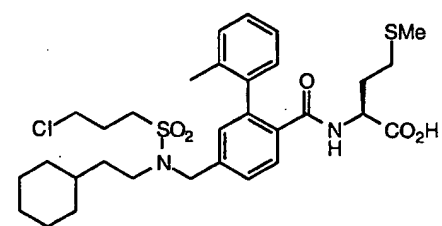


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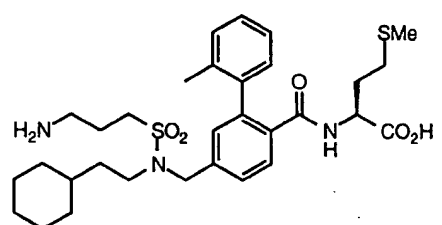
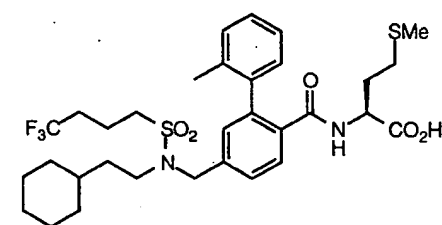


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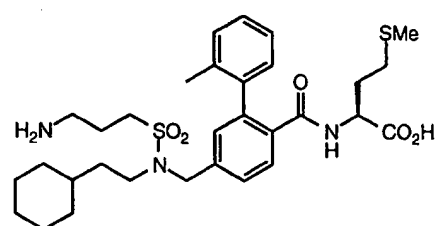
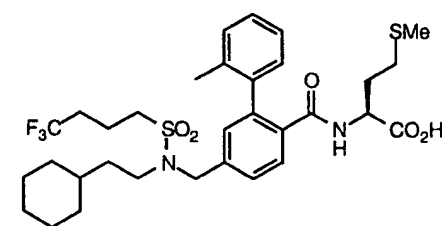
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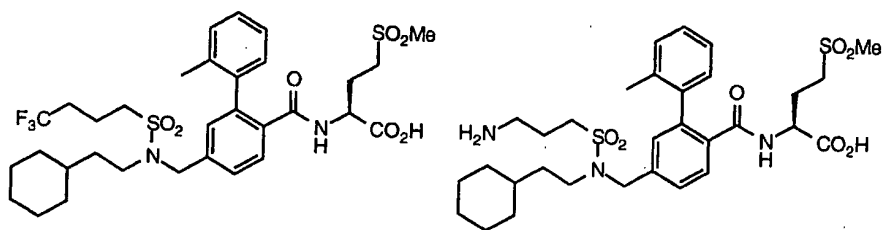


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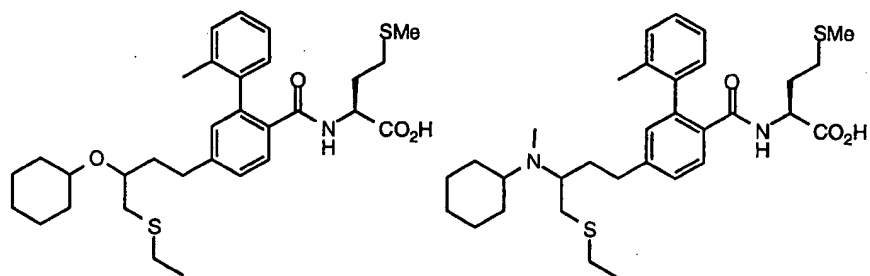
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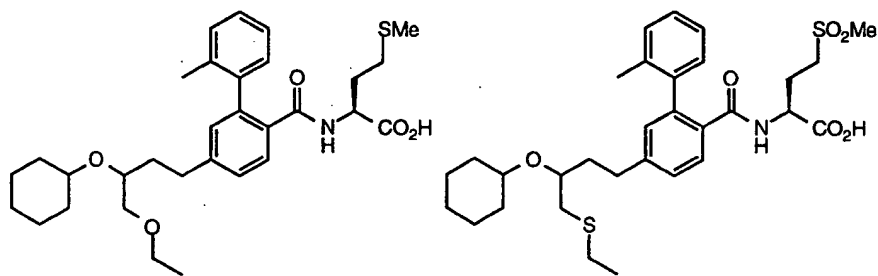


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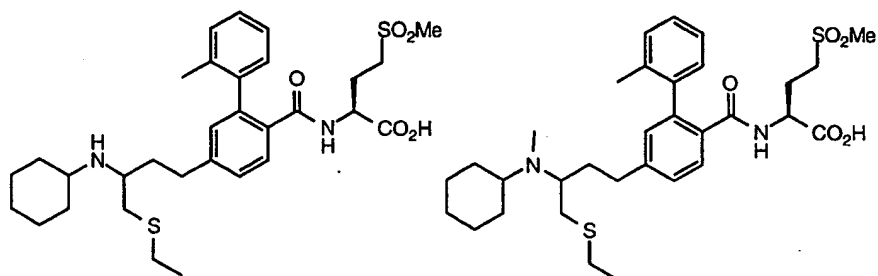
Table 9. Hydrocarbons of the Type A(B)CH₂-L₁

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1 2

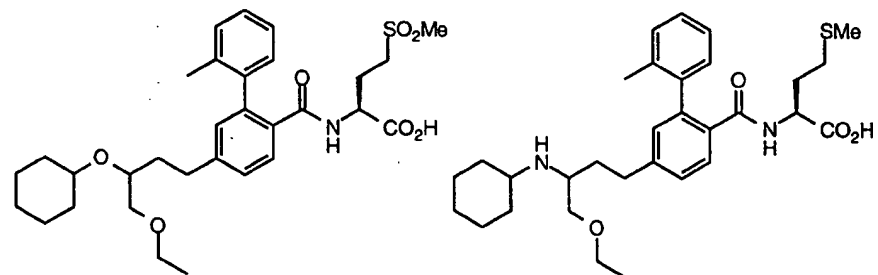


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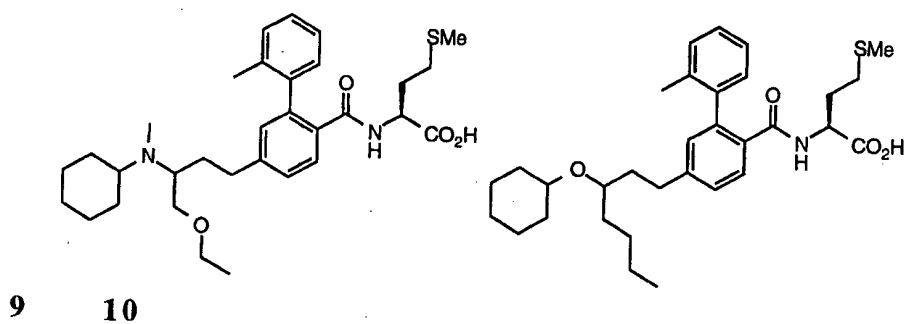
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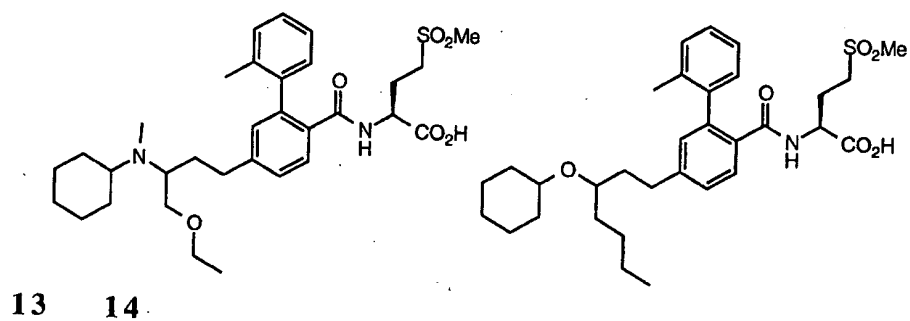
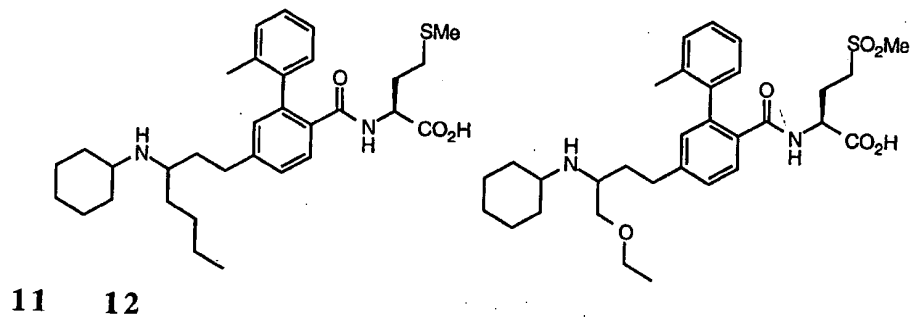


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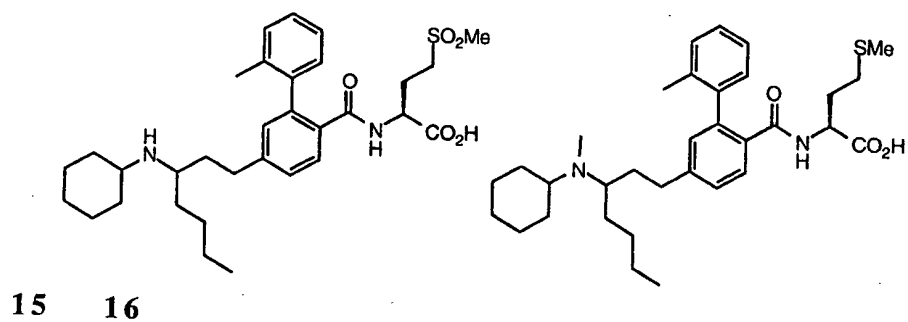
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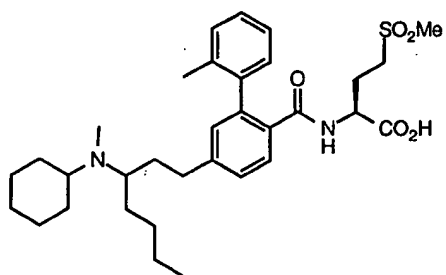


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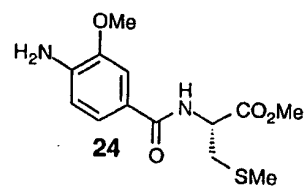
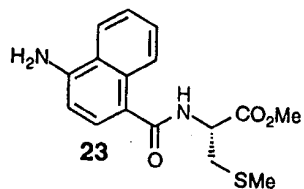
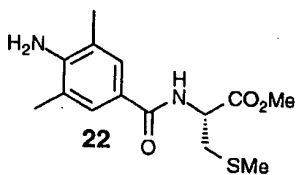
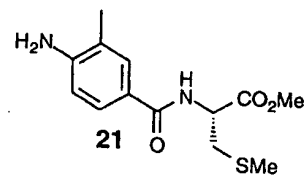
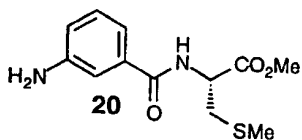
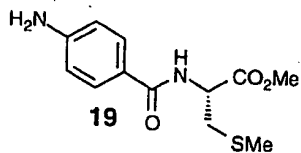
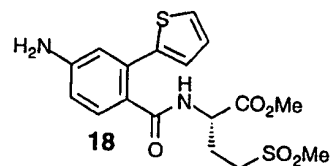
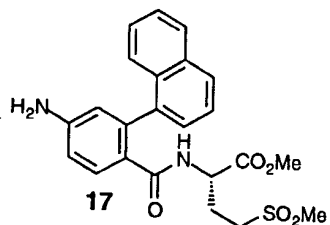
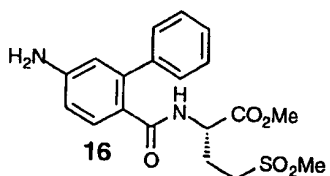
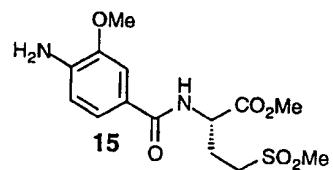
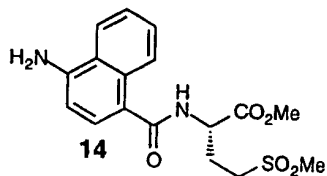
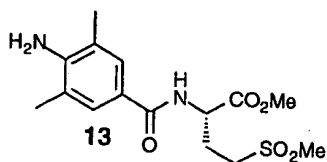
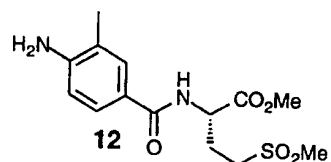
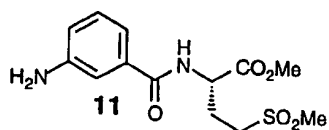
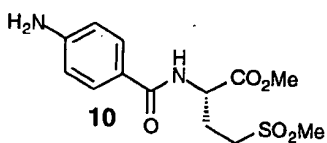
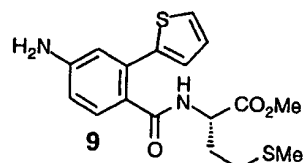
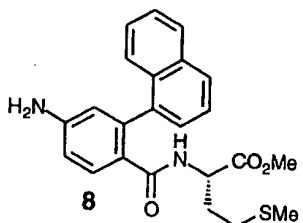
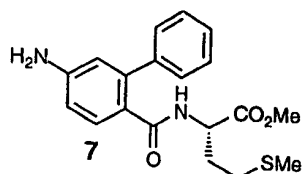
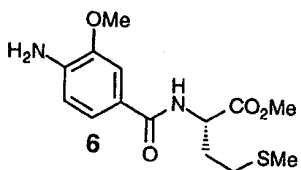
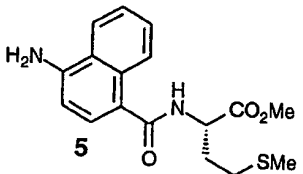
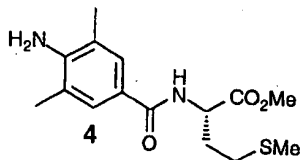
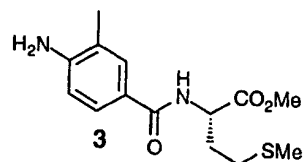
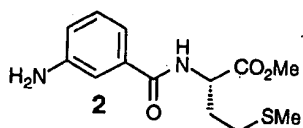
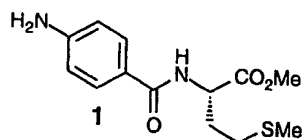


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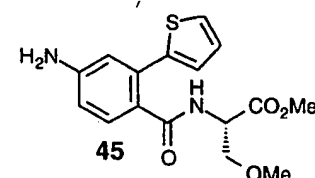
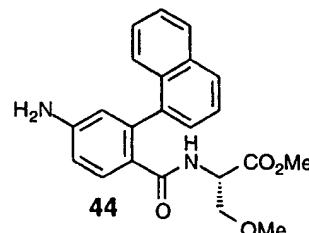
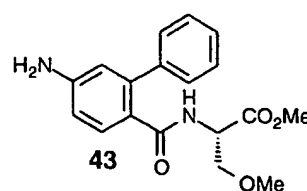
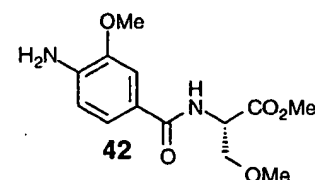
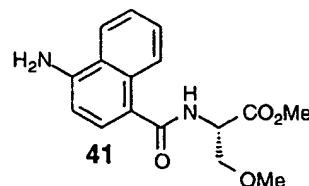
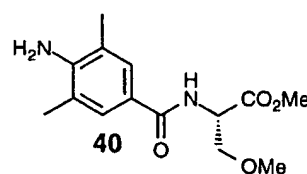
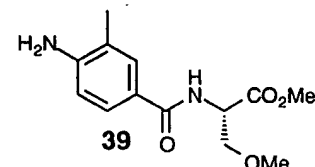
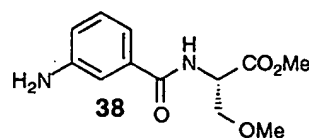
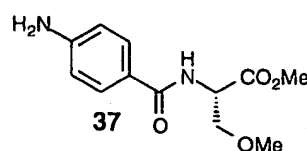
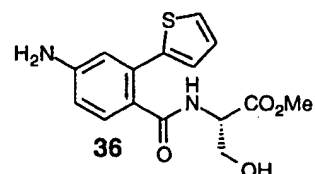
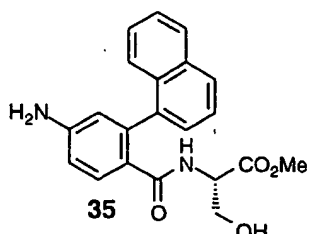
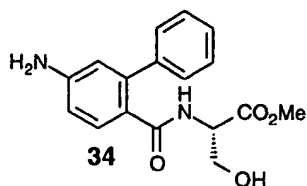
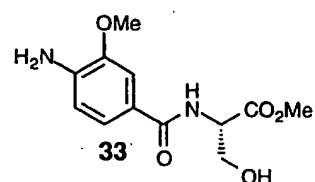
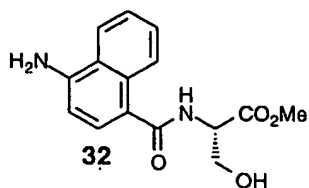
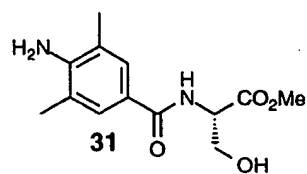
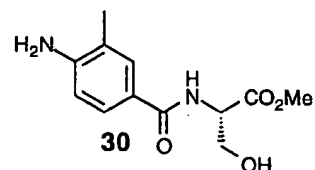
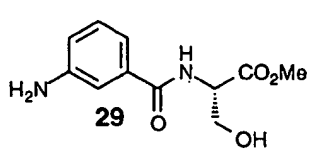
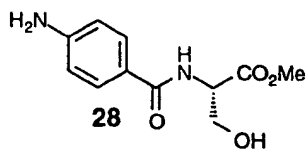
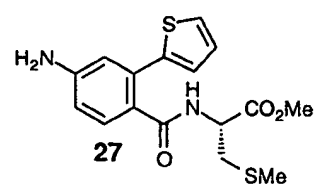
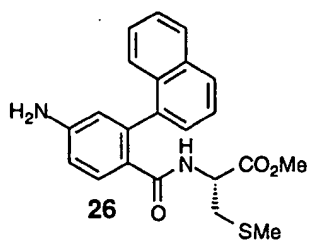
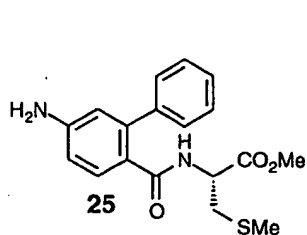


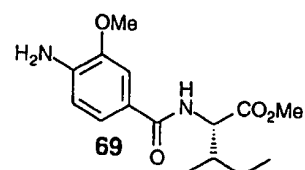
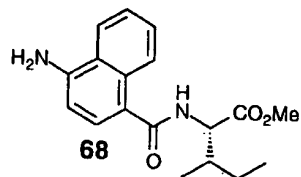
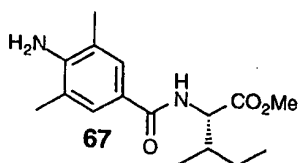
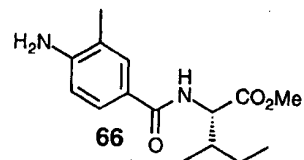
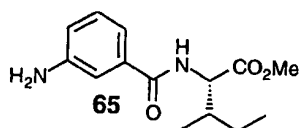
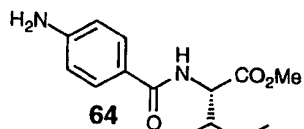
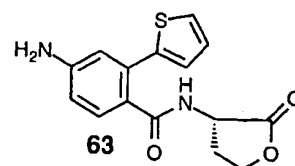
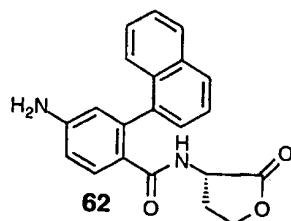
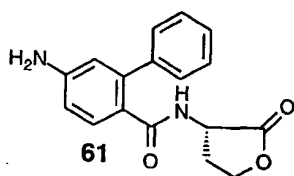
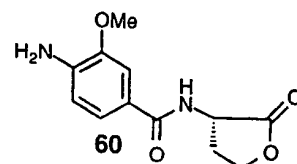
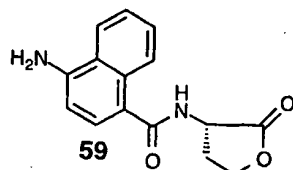
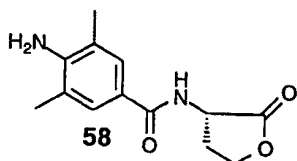
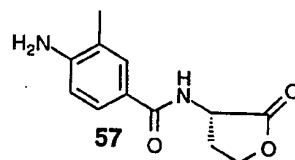
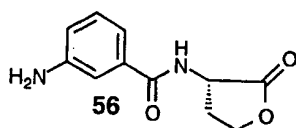
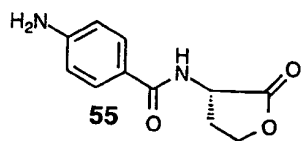
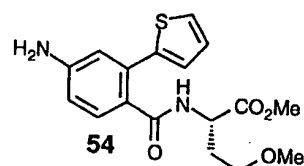
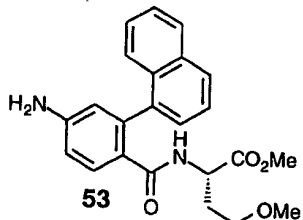
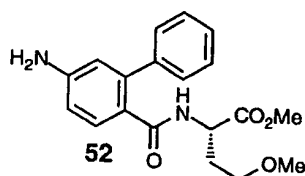
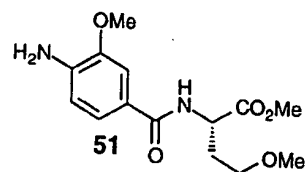
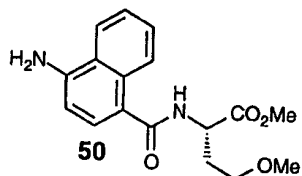
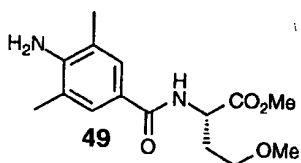
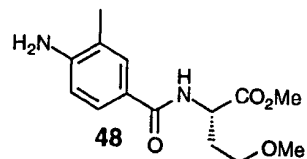
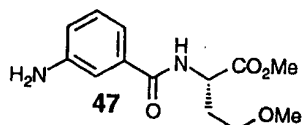
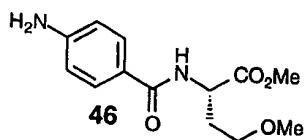


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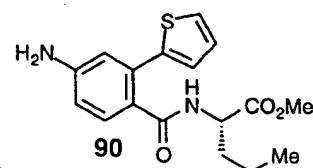
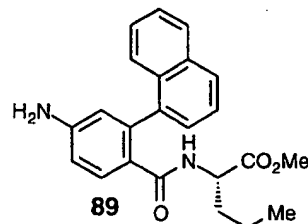
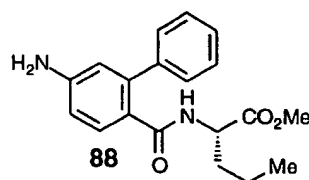
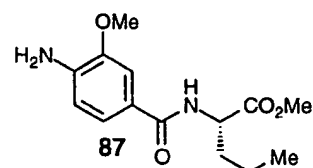
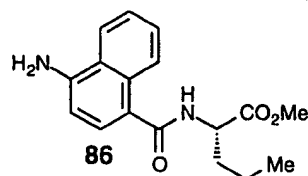
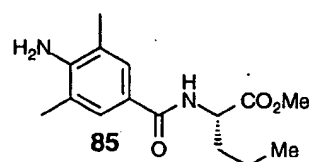
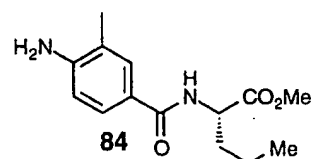
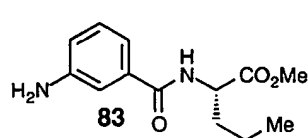
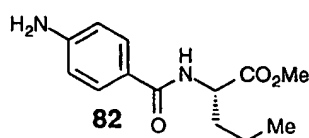
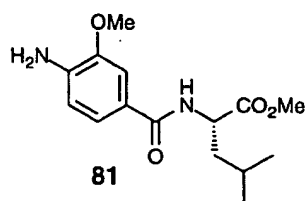
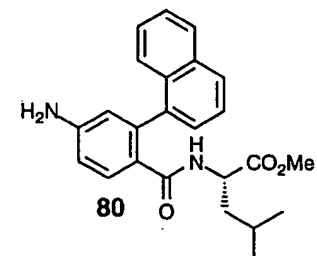
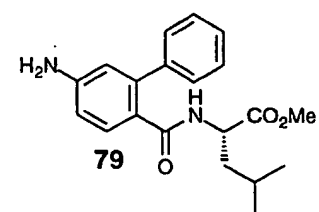
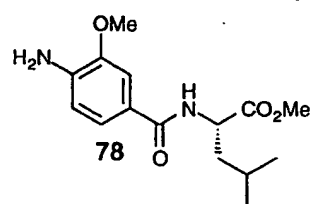
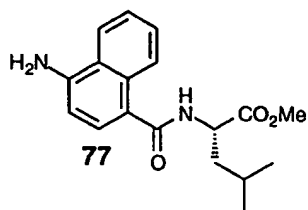
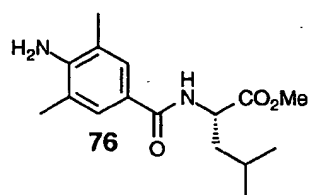
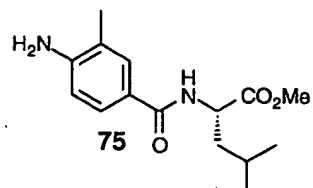
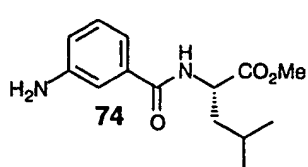
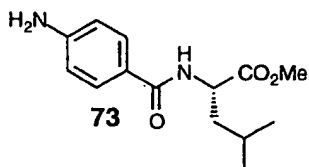
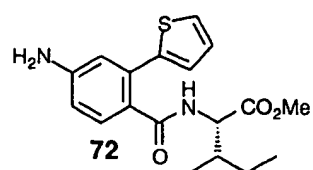
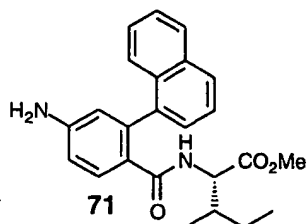
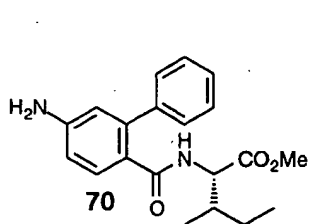
2520 Table 10. Amines of the type B-NH₂

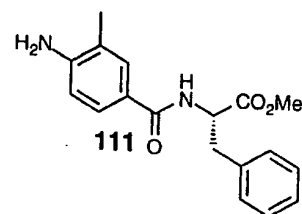
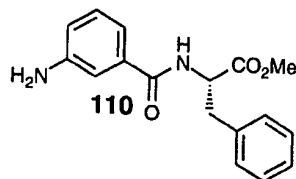
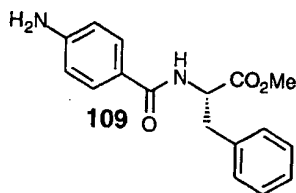
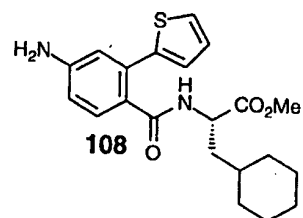
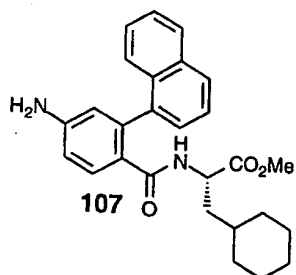
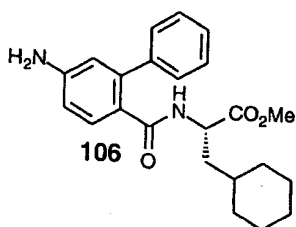
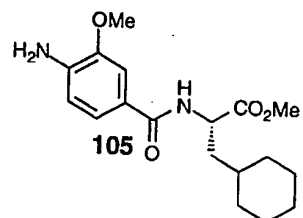
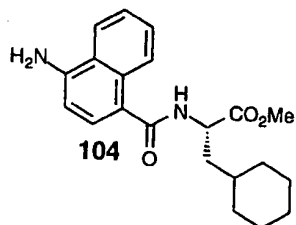
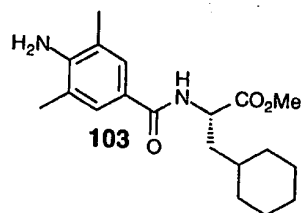
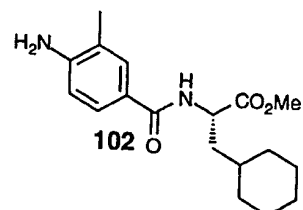
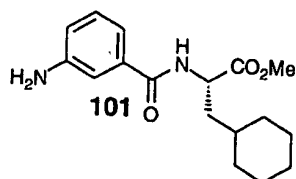
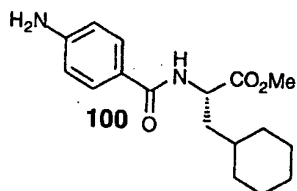
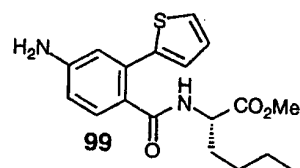
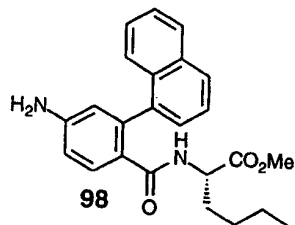
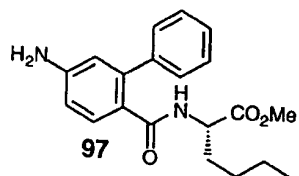
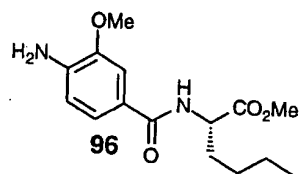
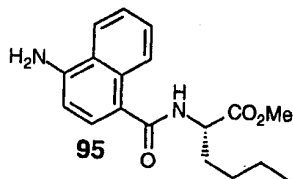
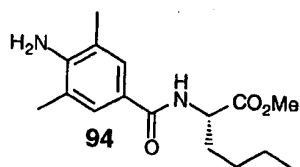
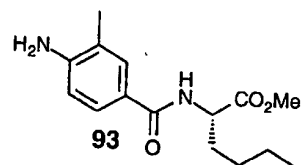
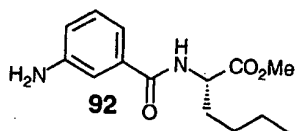
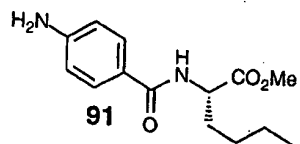
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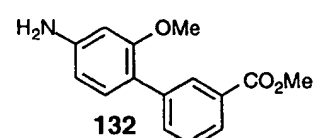
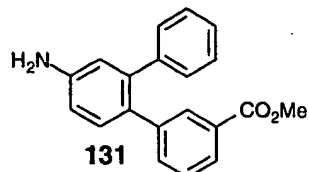
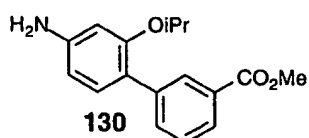
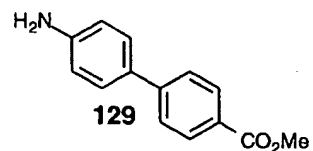
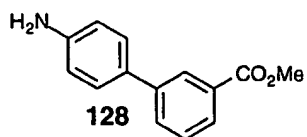
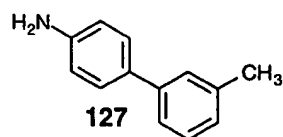
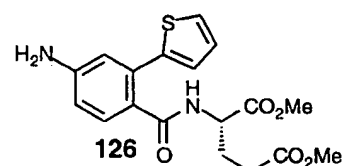
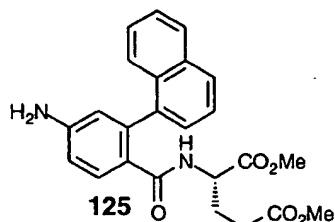
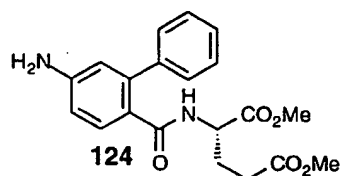
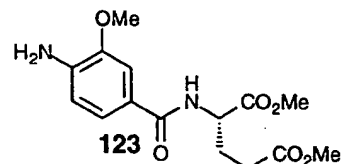
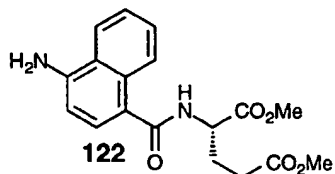
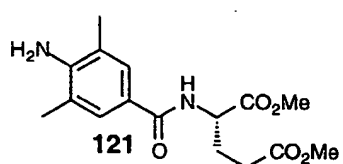
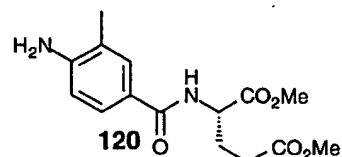
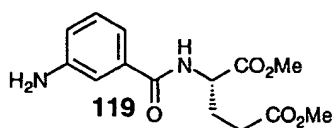
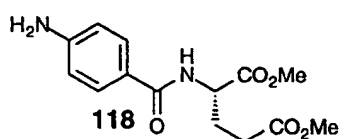
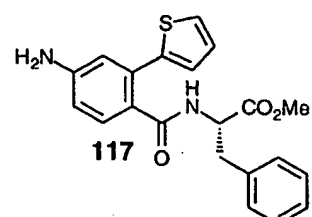
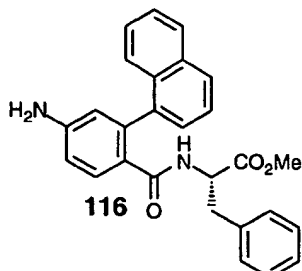
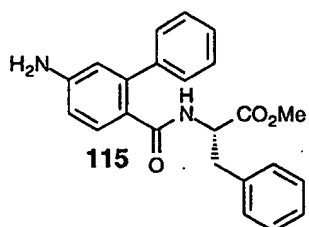
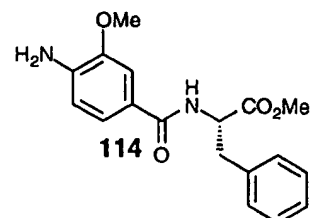
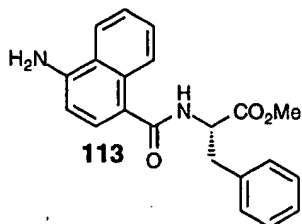
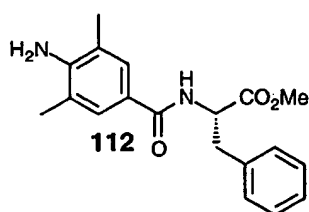


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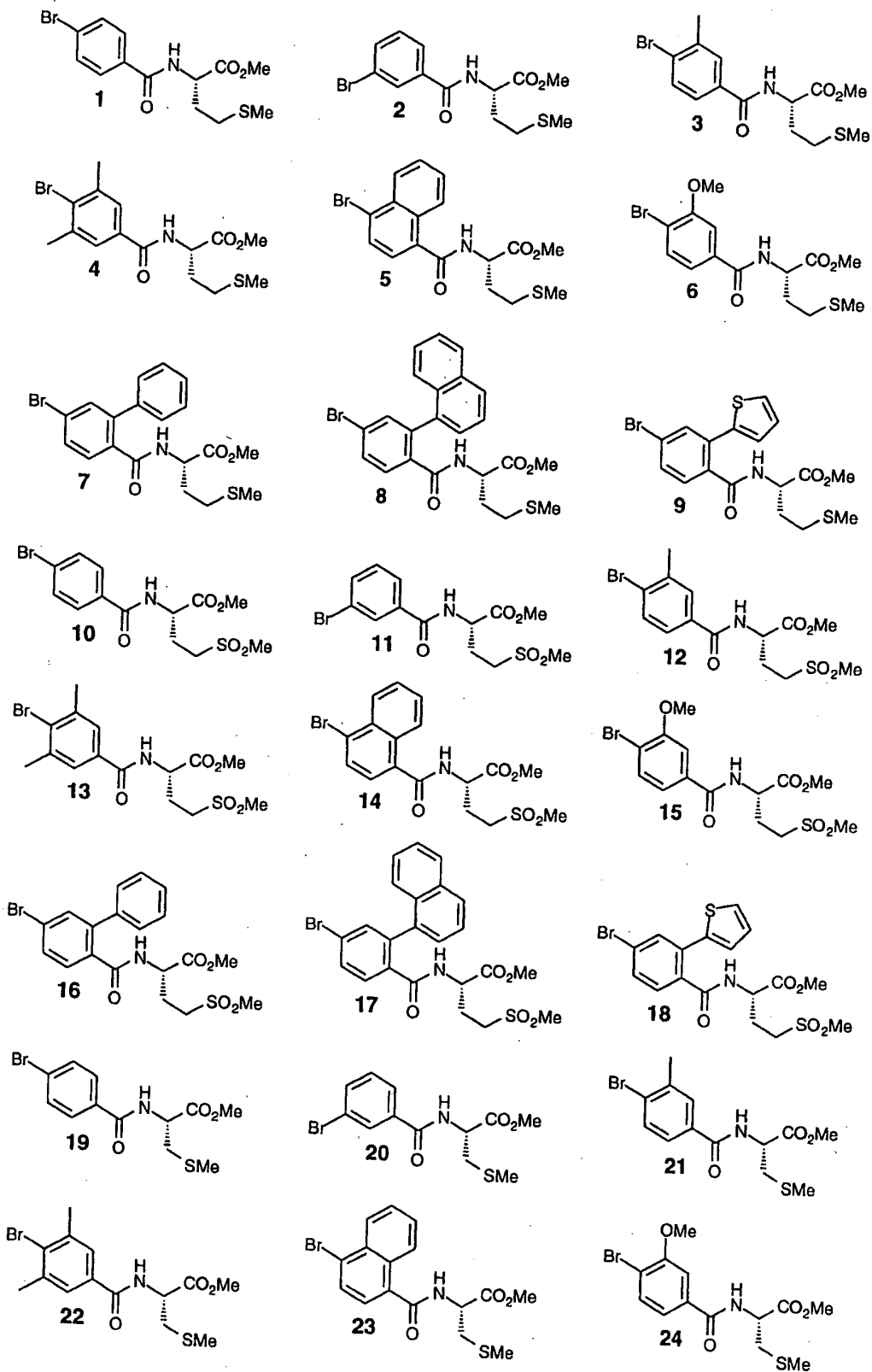
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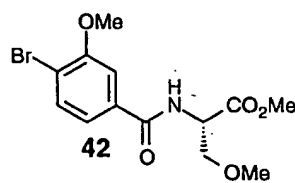
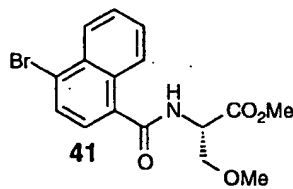
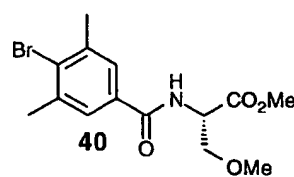
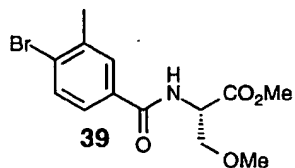
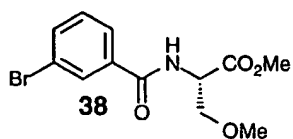
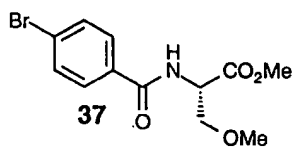
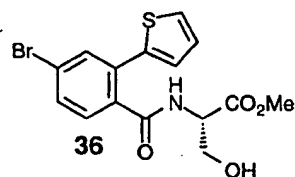
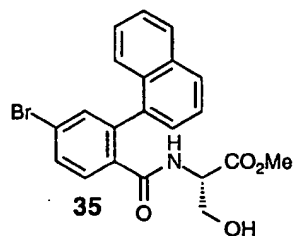
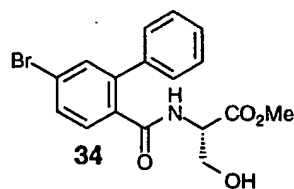
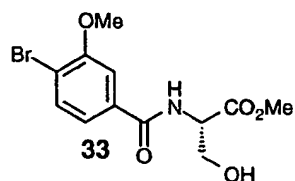
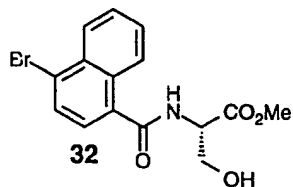
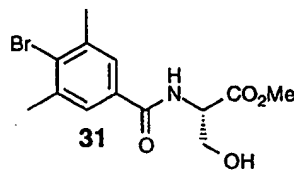
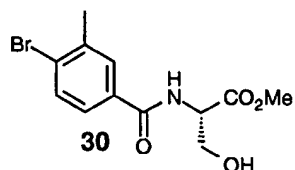
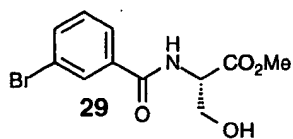
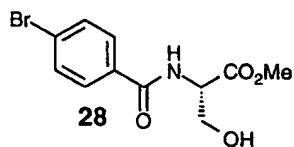
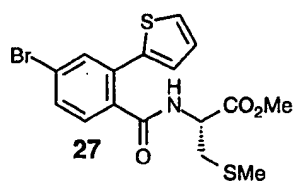
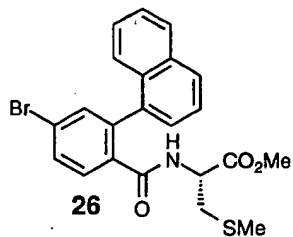
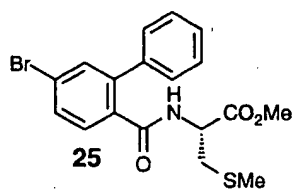
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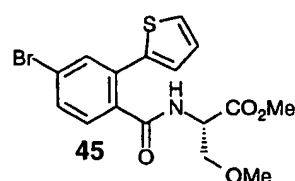
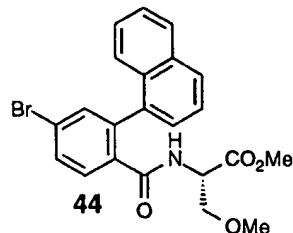
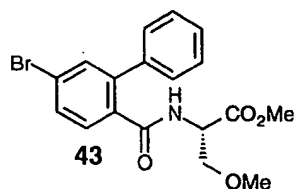
Table 11. Bromides of the type B-Br

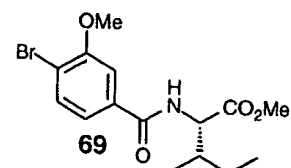
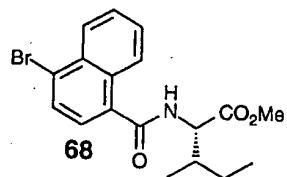
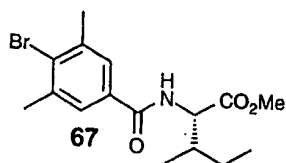
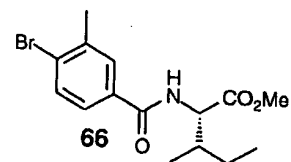
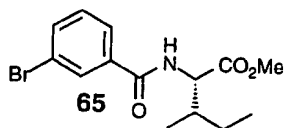
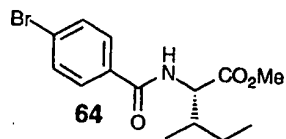
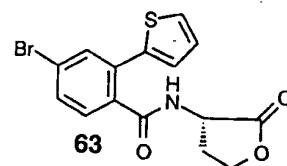
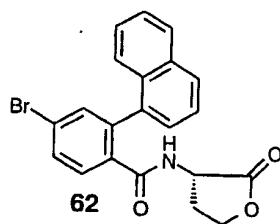
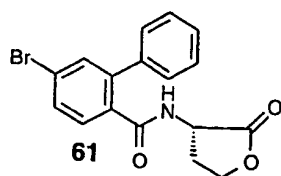
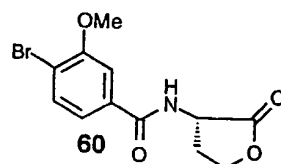
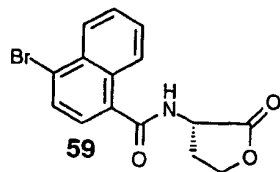
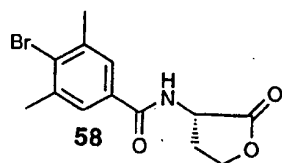
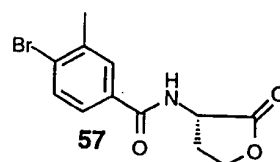
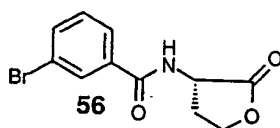
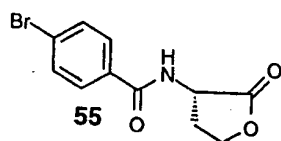
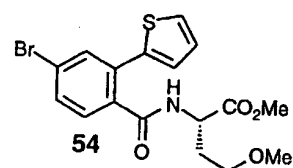
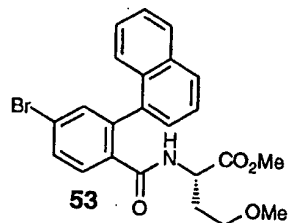
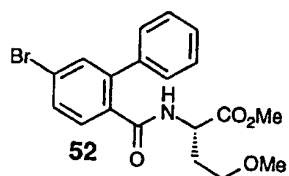
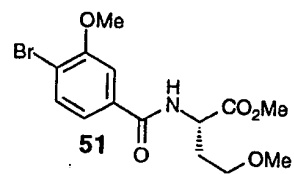
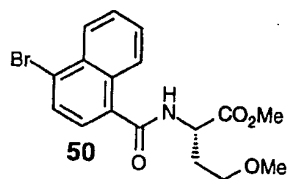
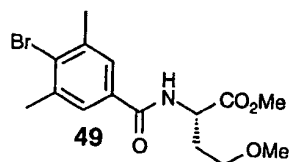
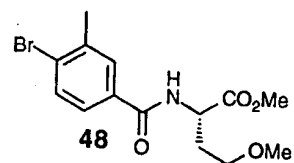
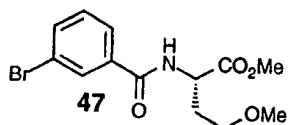
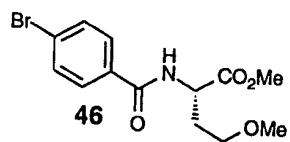


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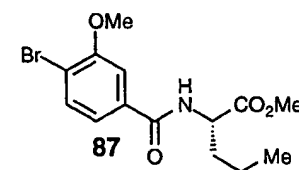
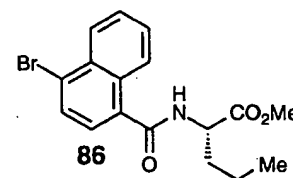
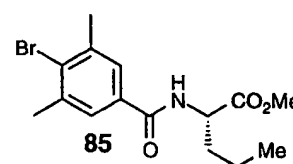
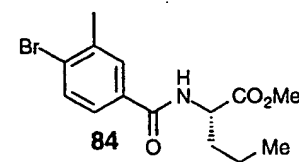
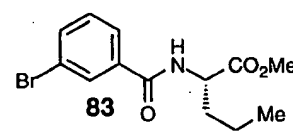
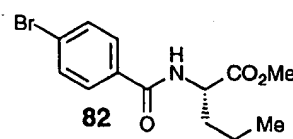
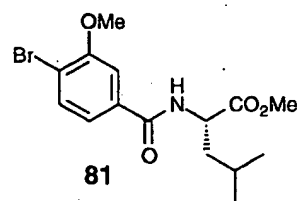
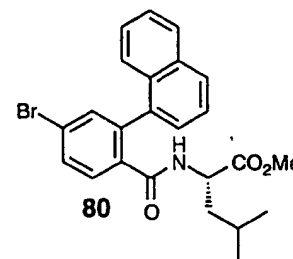
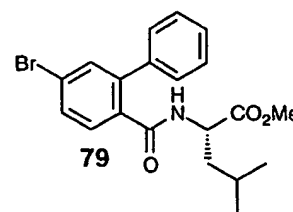
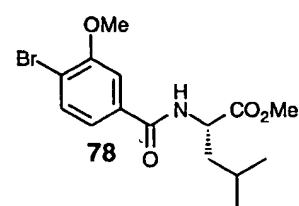
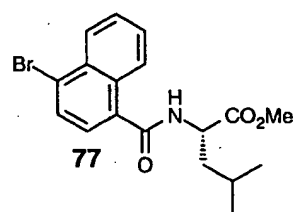
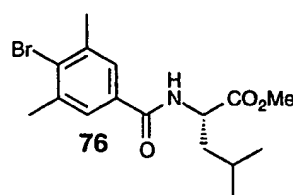
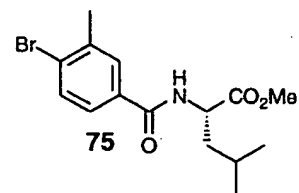
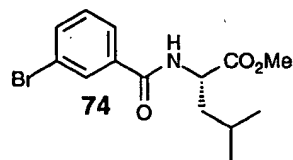
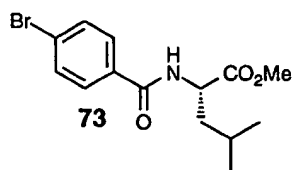
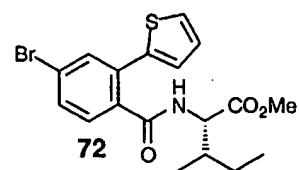
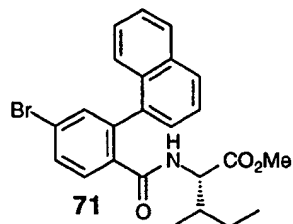
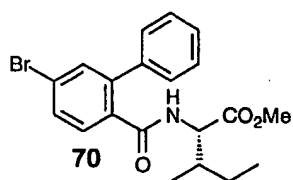
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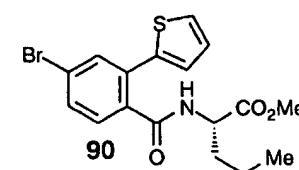
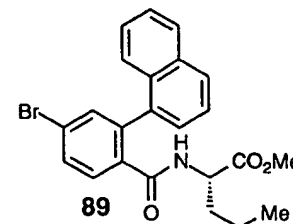
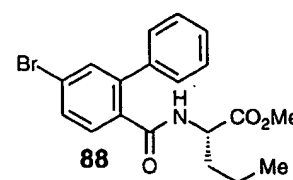


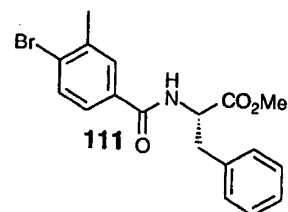
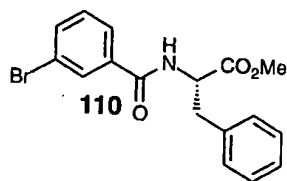
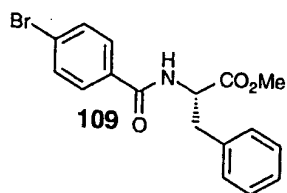
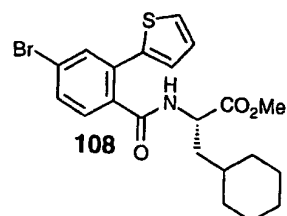
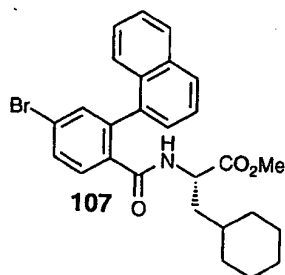
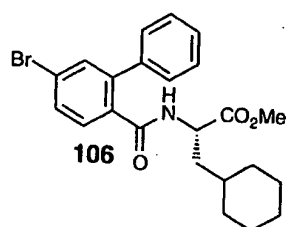
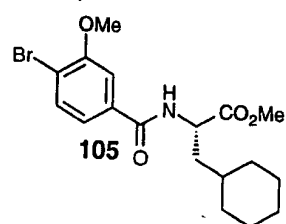
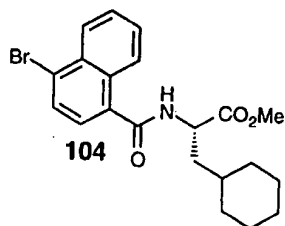
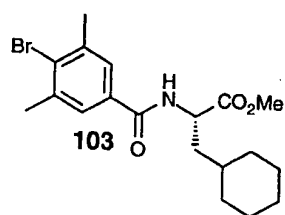
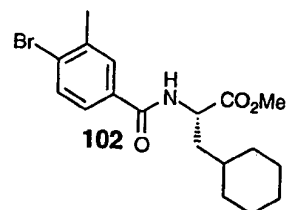
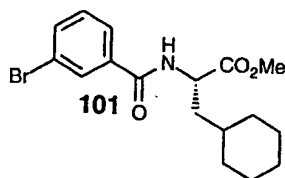
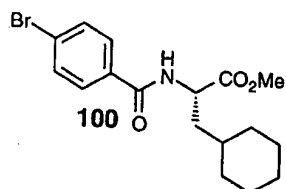
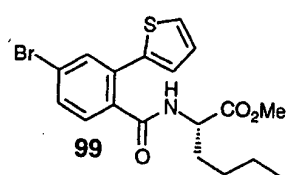
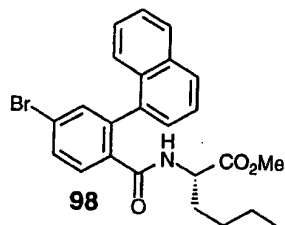
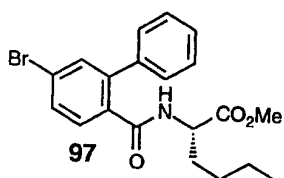
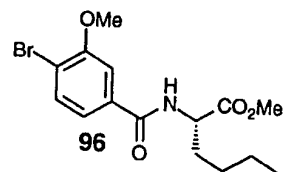
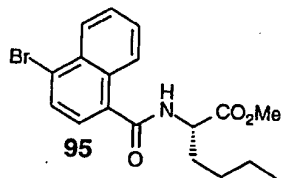
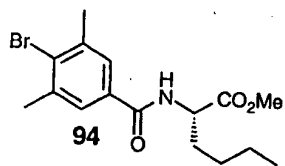
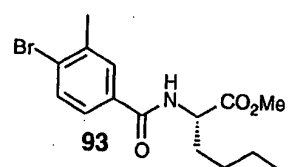
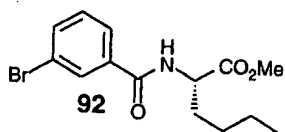
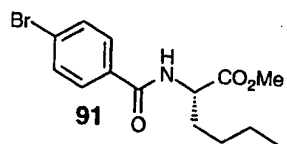
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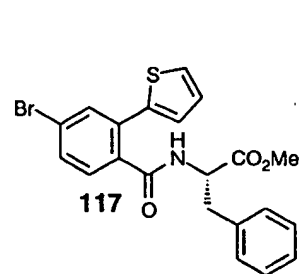
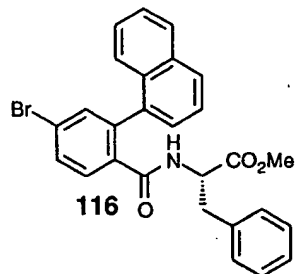
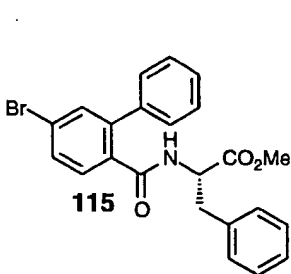
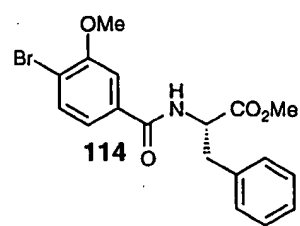
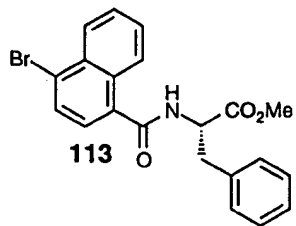
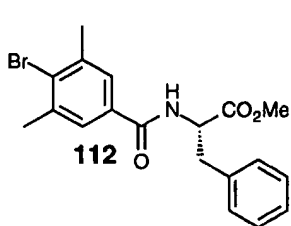


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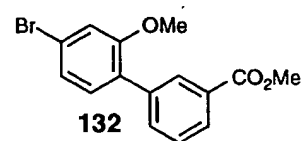
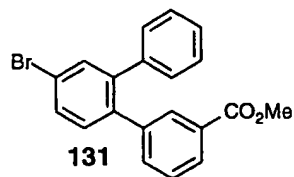
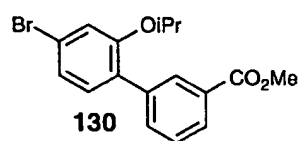
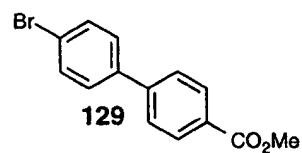
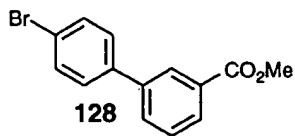
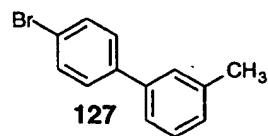
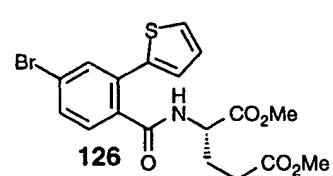
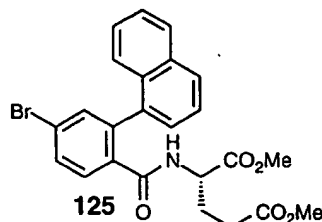
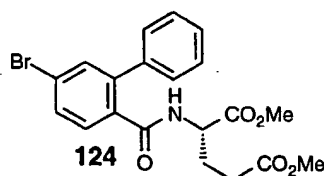
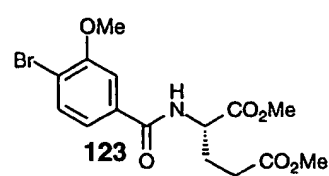
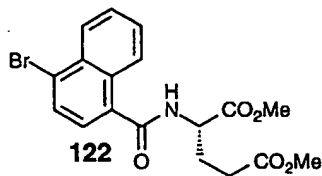
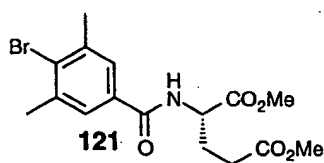
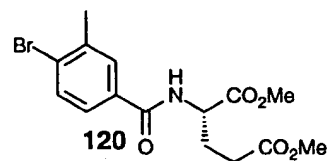
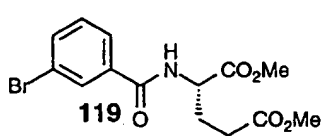
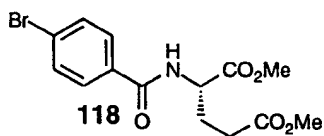




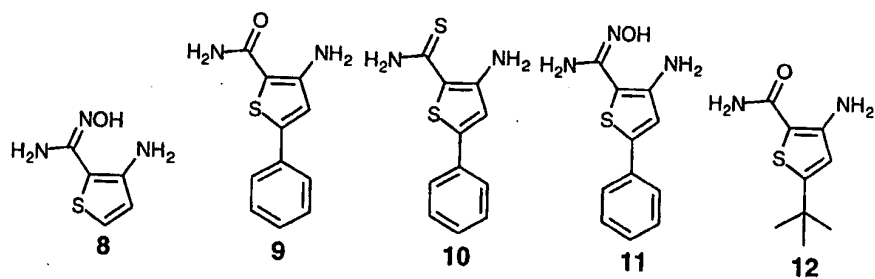
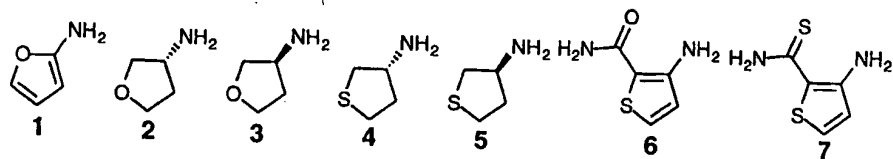
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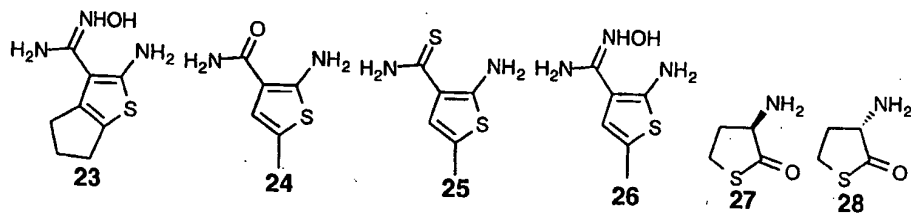
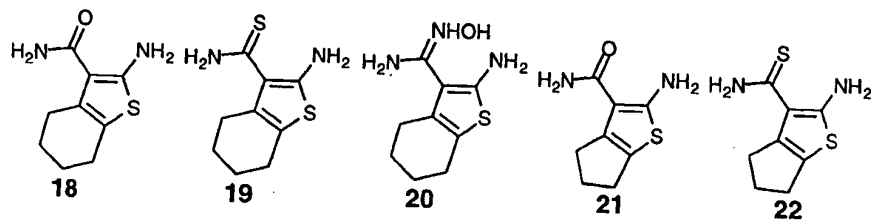
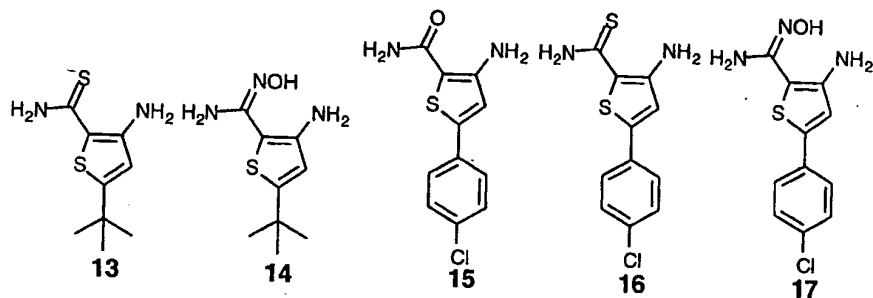
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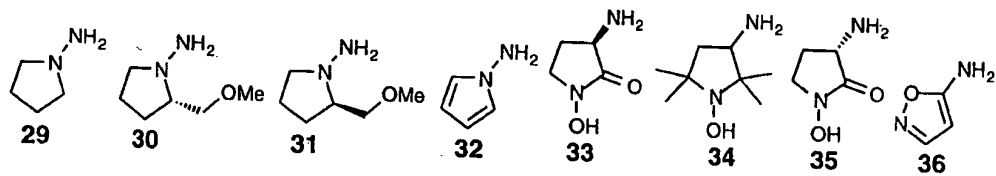
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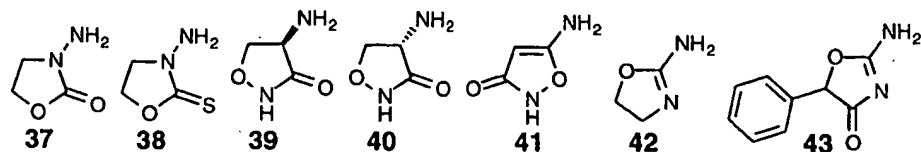
Table 12. Amines of the type A-NH₂

2615

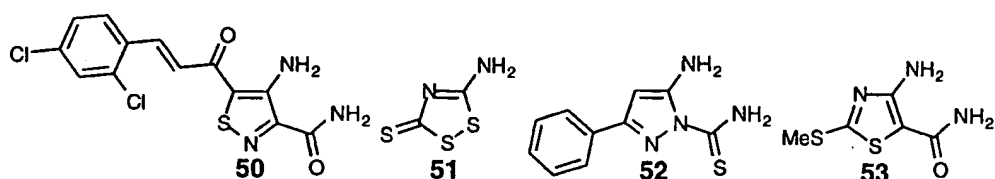
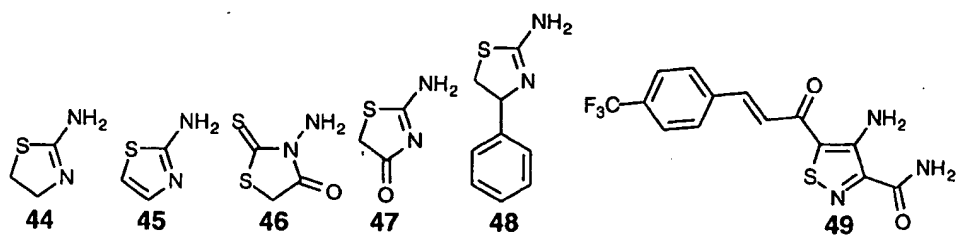


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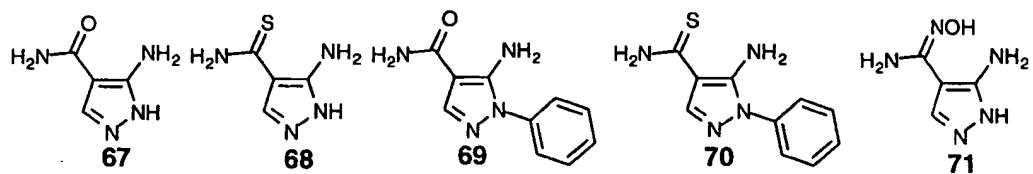
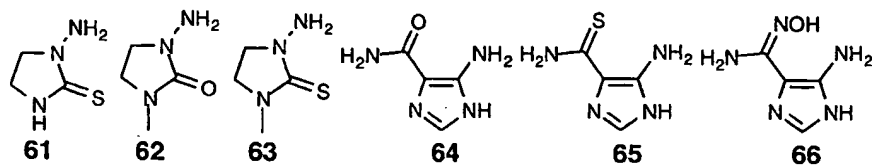
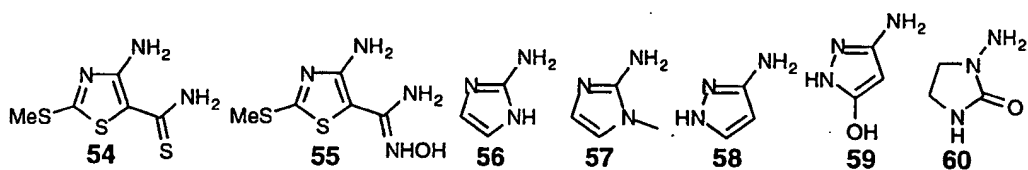




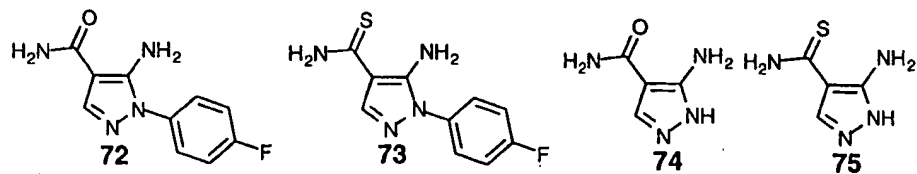
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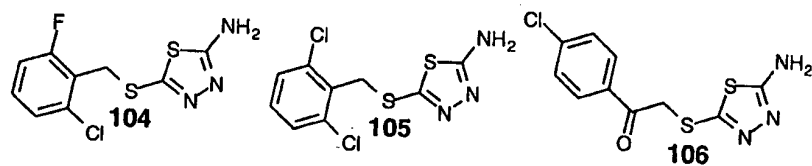
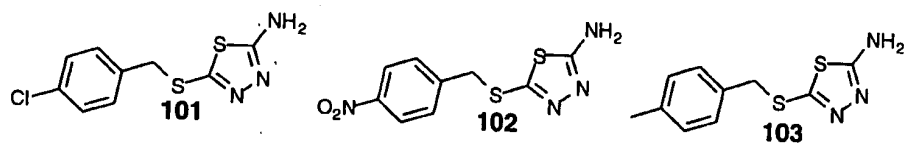
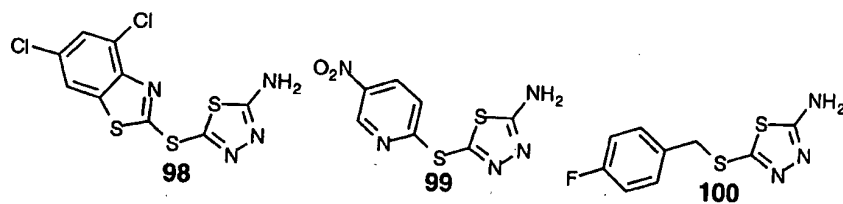
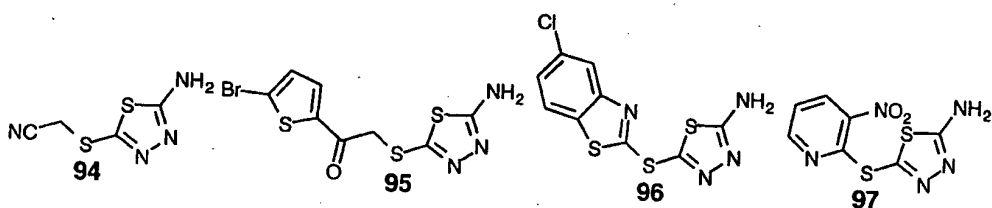
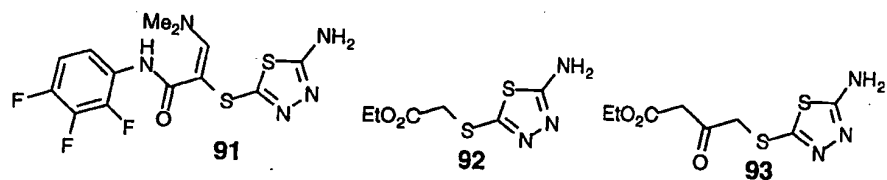
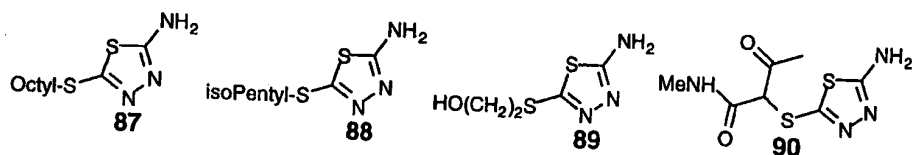
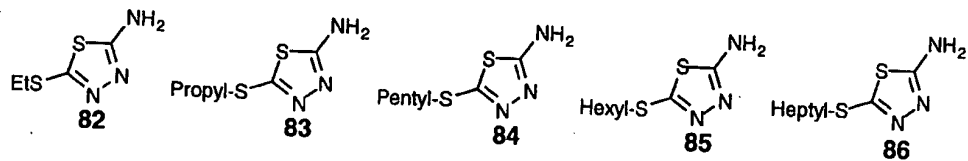
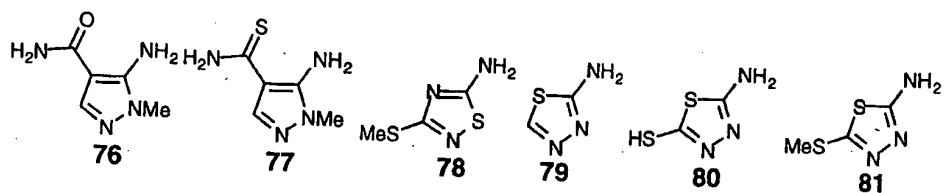


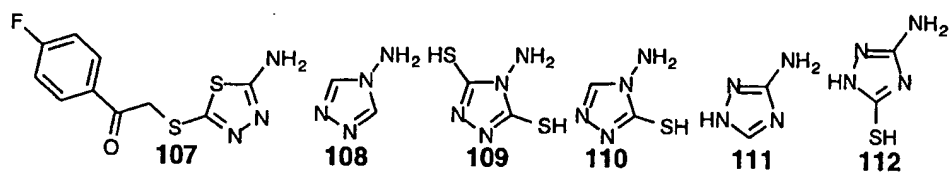
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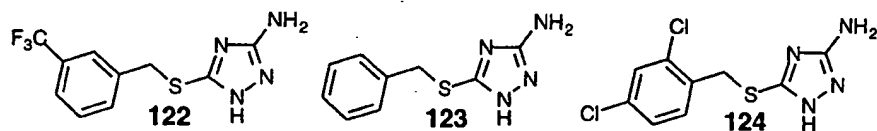
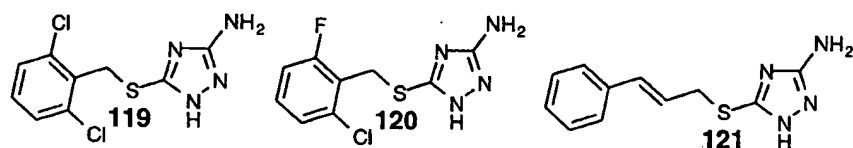
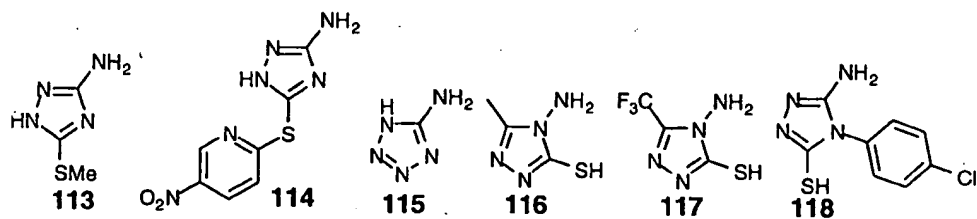
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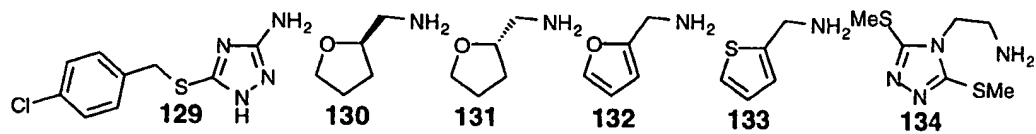
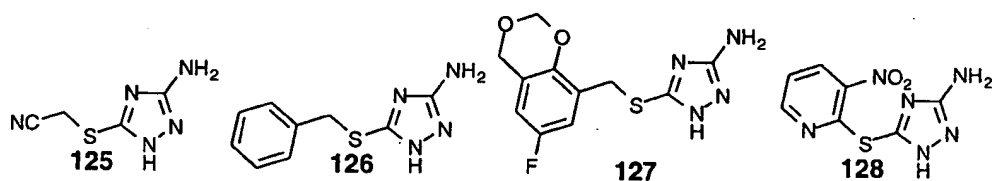




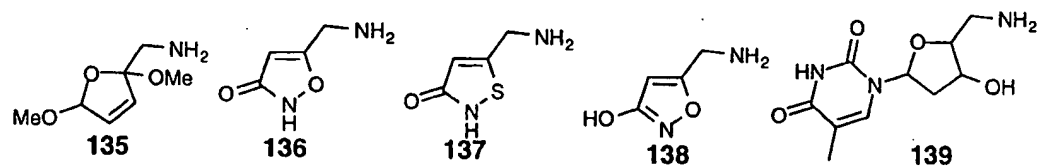
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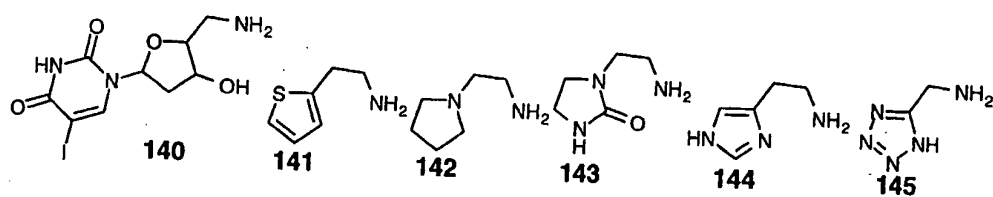


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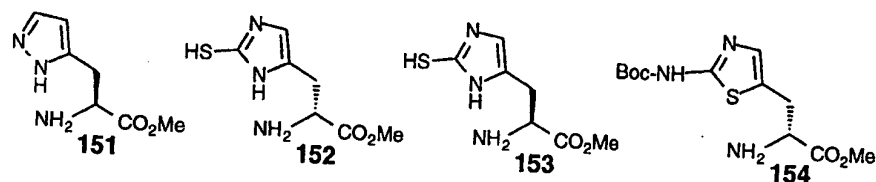
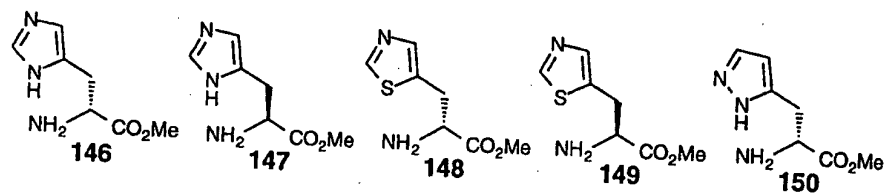


2665

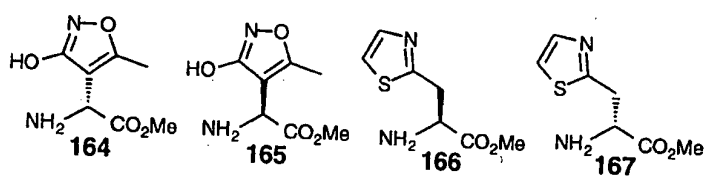
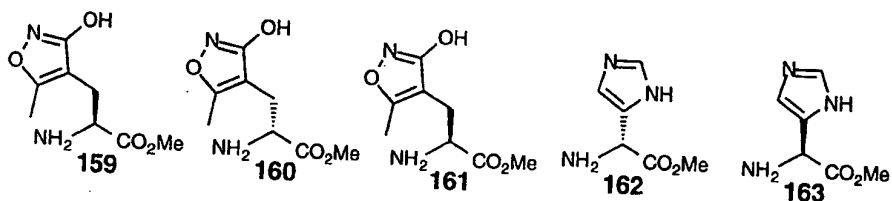
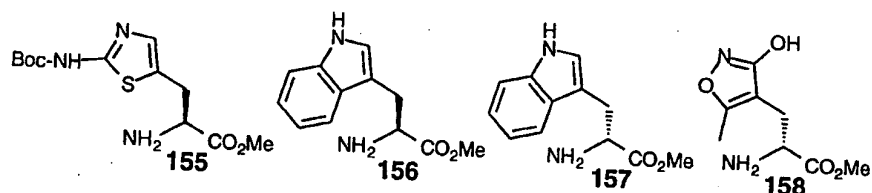




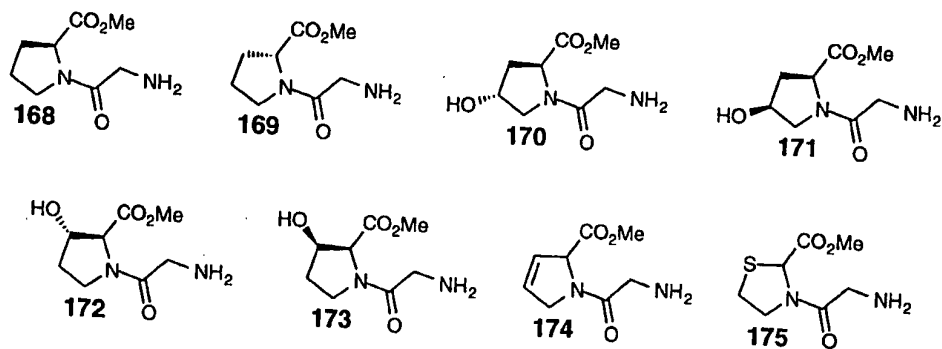
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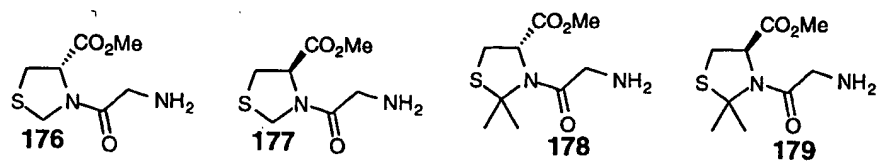


2675

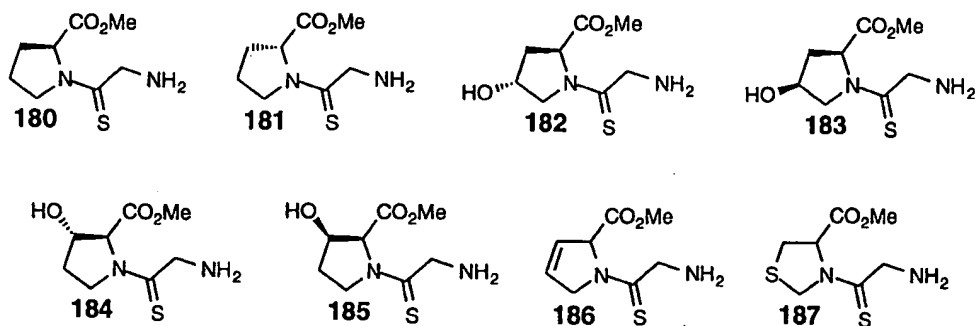


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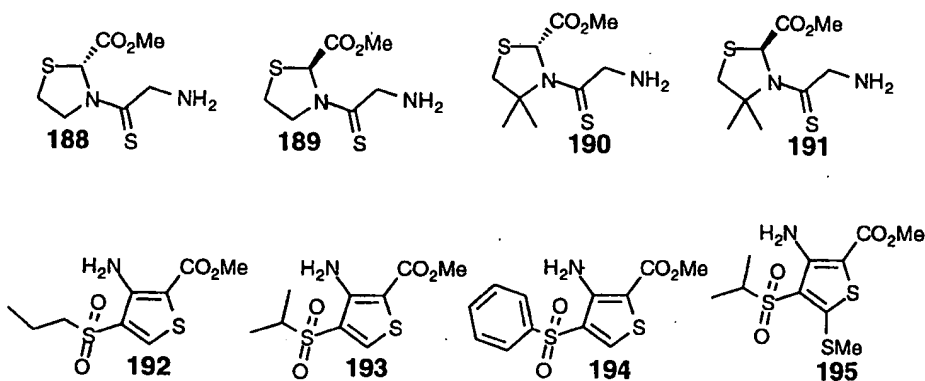




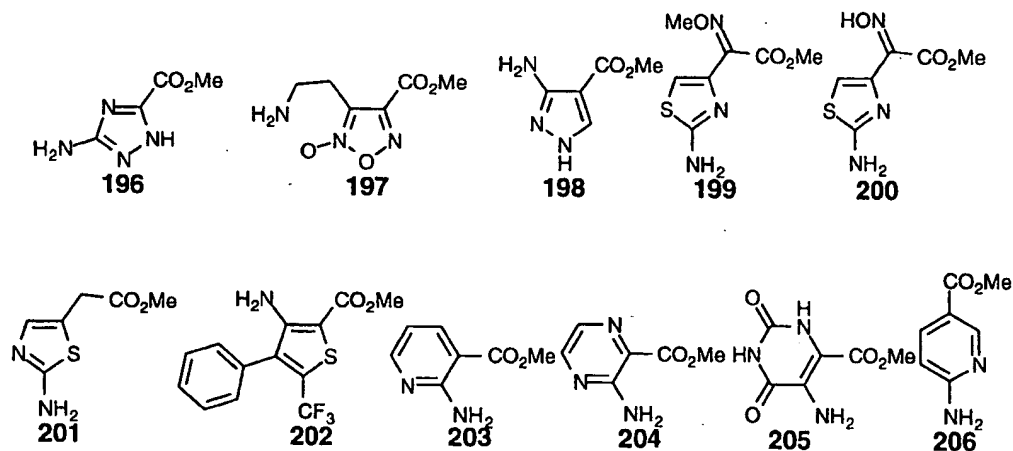
2685



2690



2695



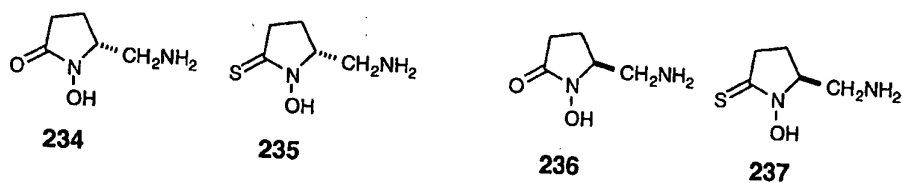
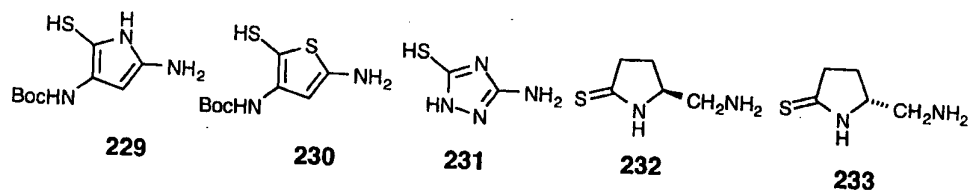
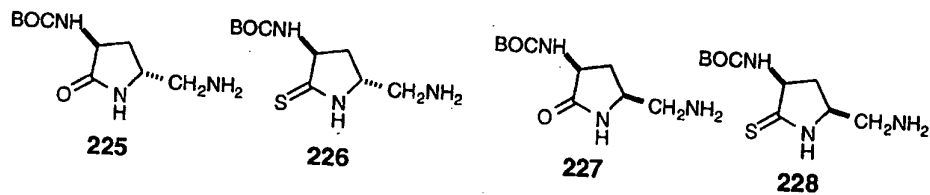
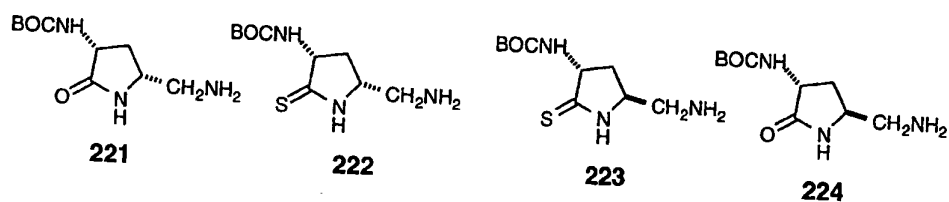
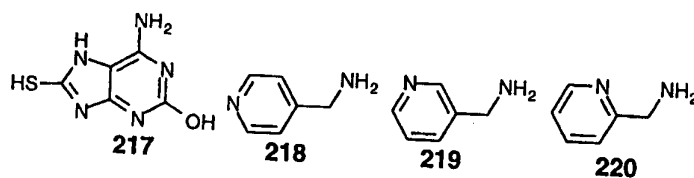
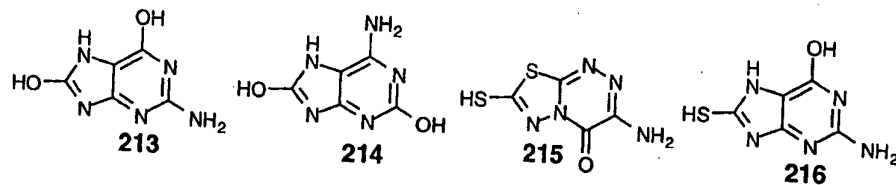
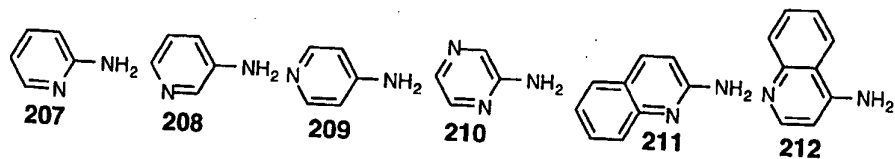
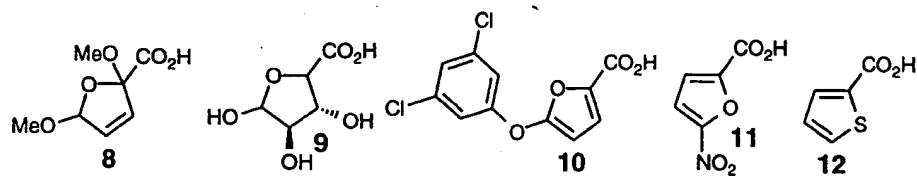
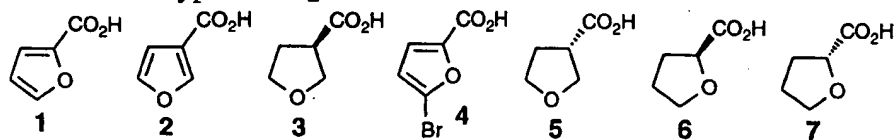
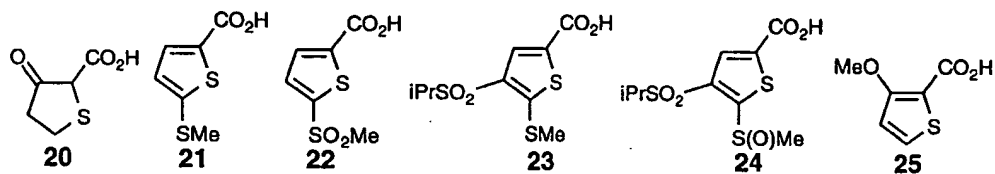
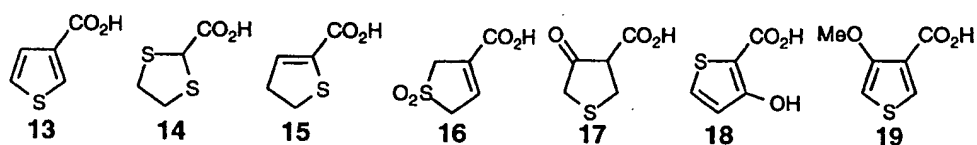
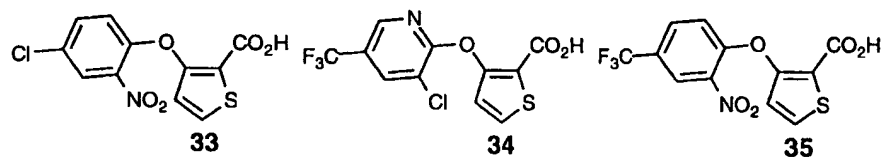
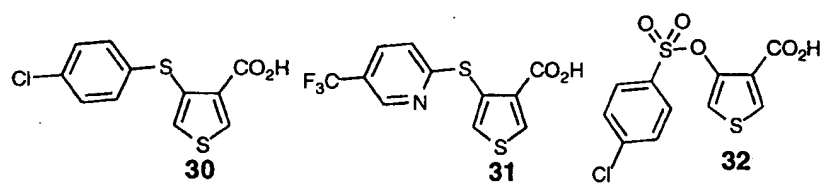
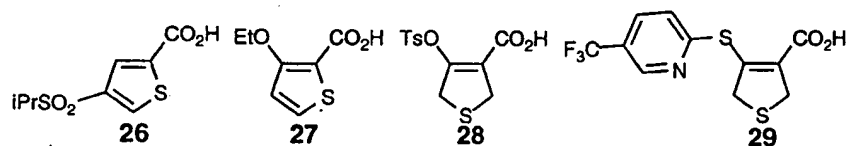


Table 13. Acids of the type A-CO₂H

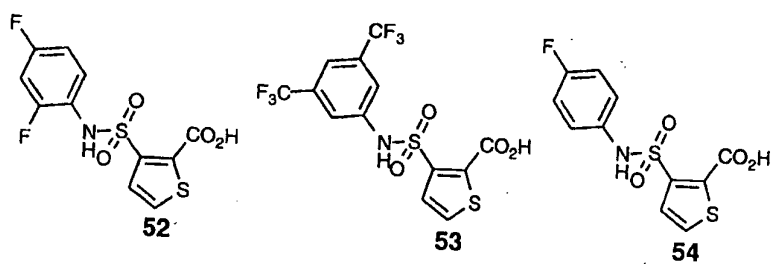
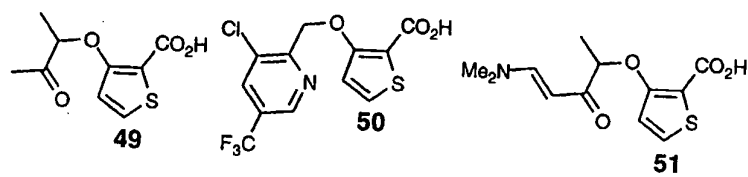
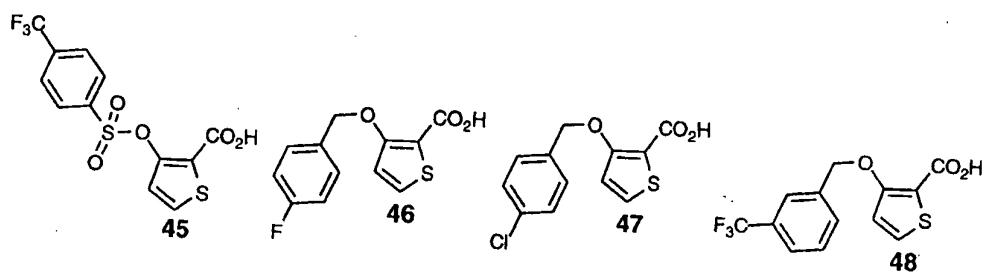
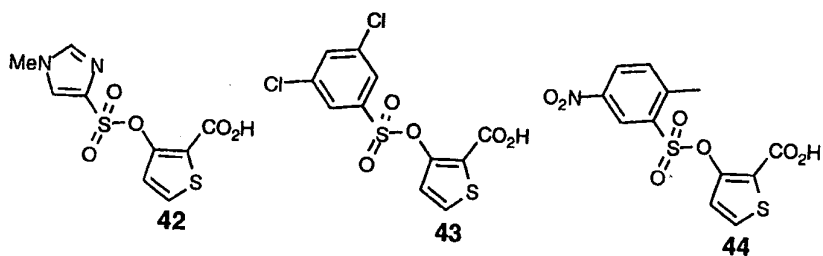
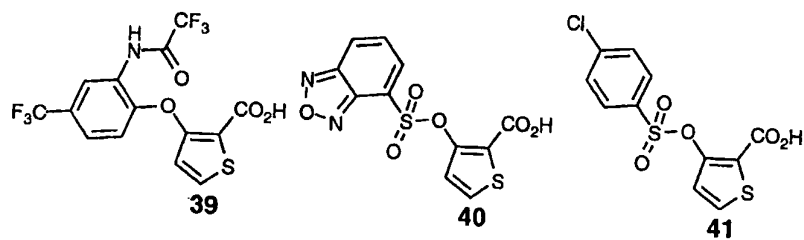
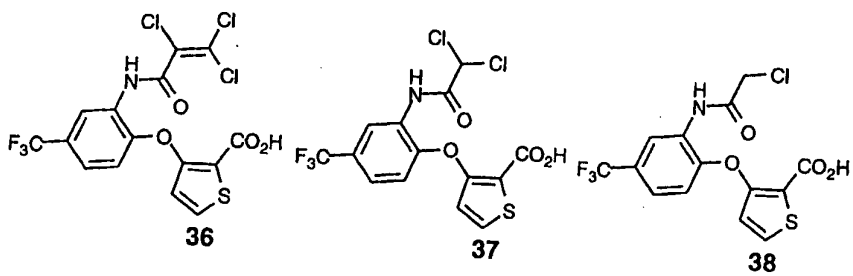
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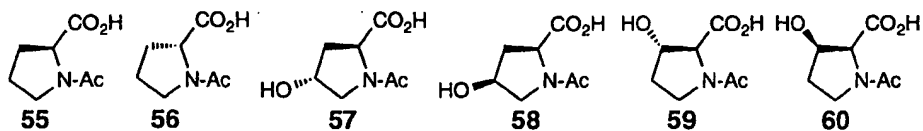


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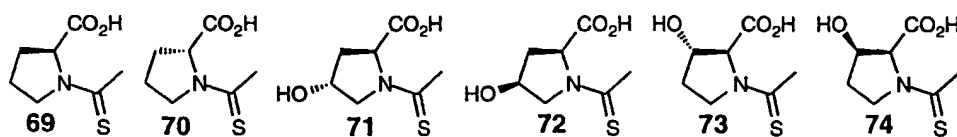
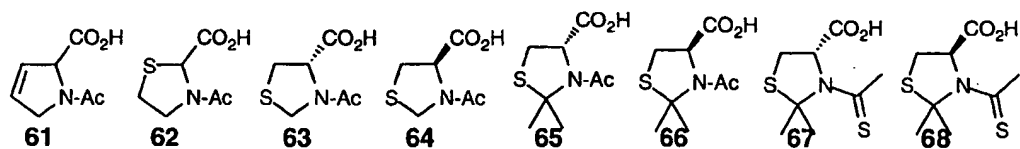


2725

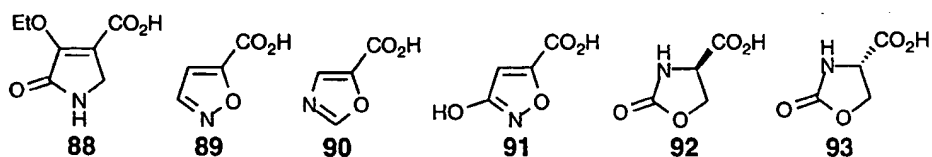
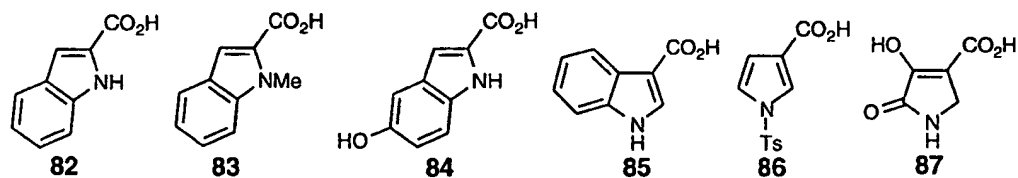
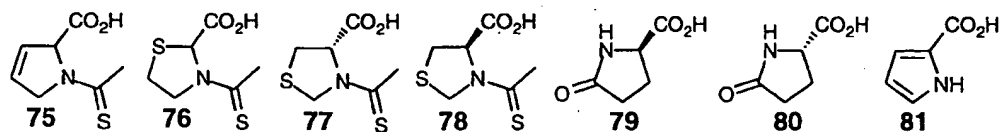




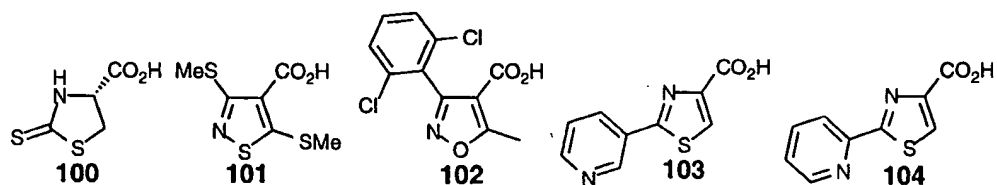
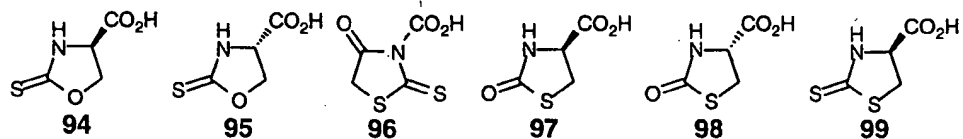
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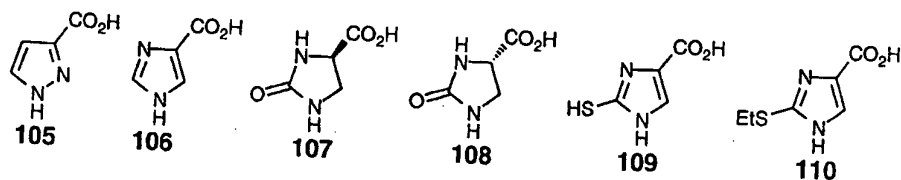
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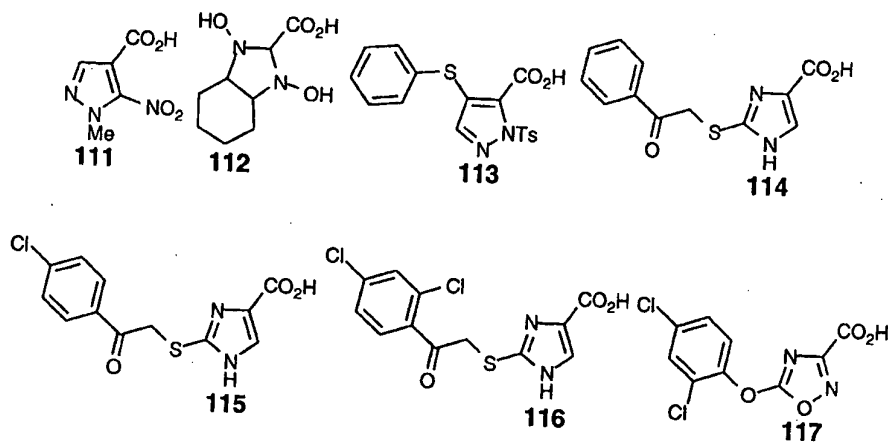
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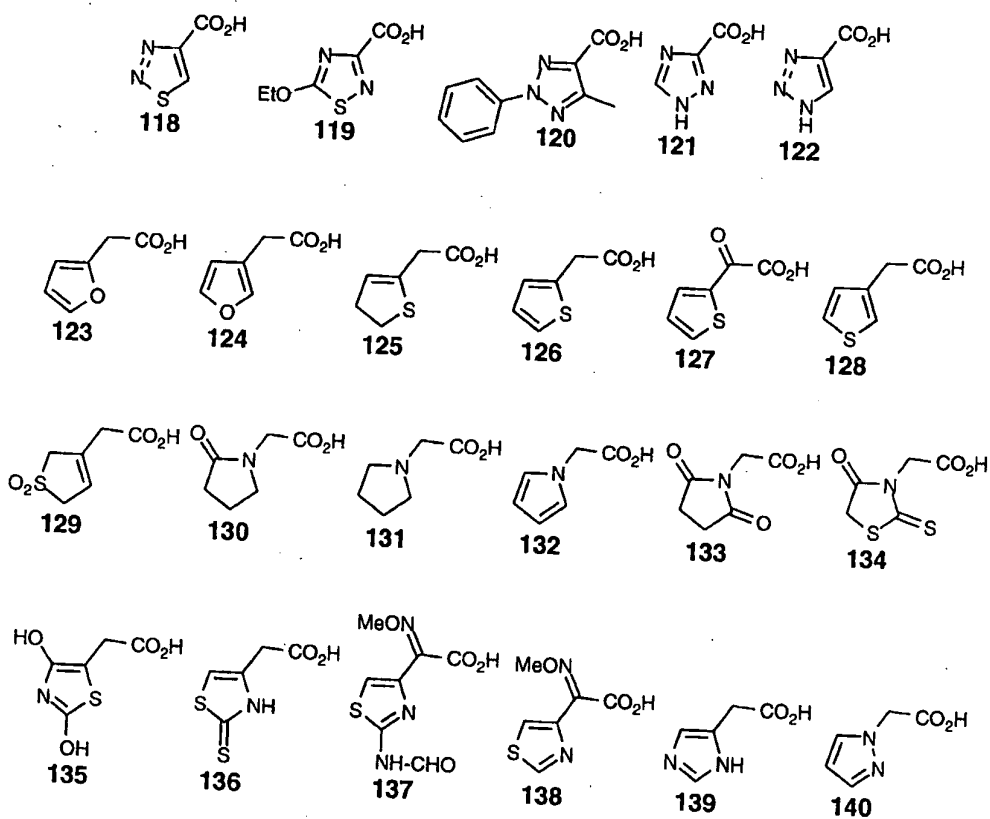
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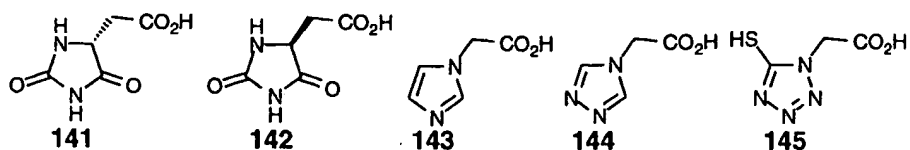


2760

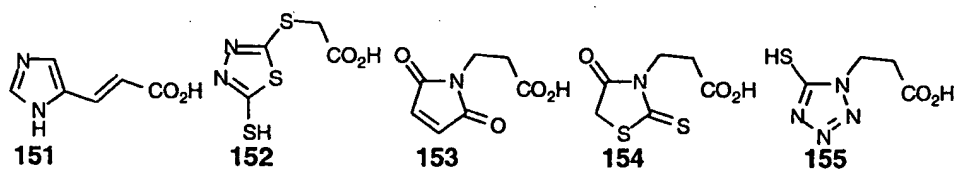
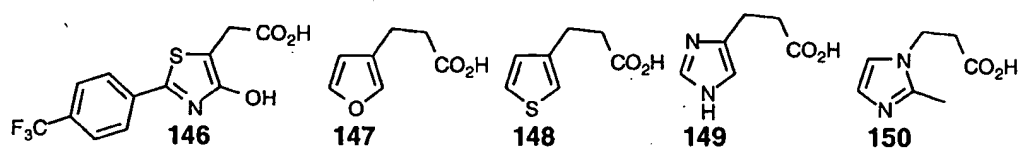


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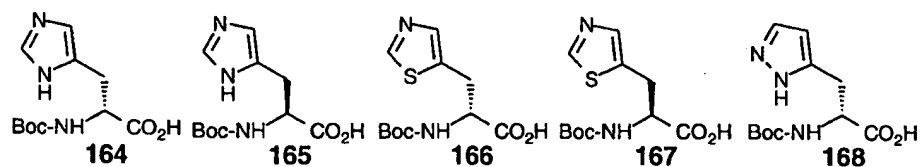
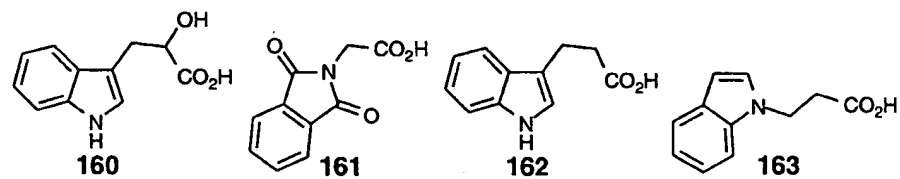
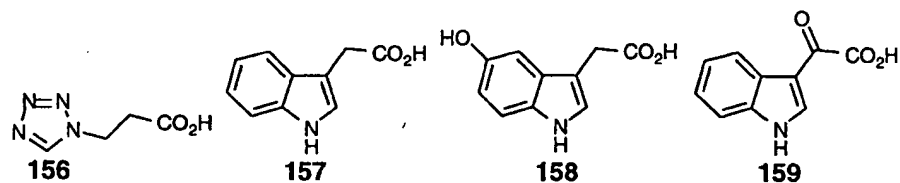




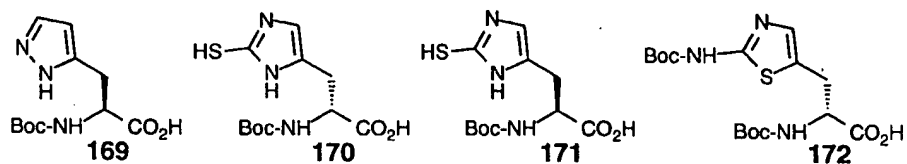
2770



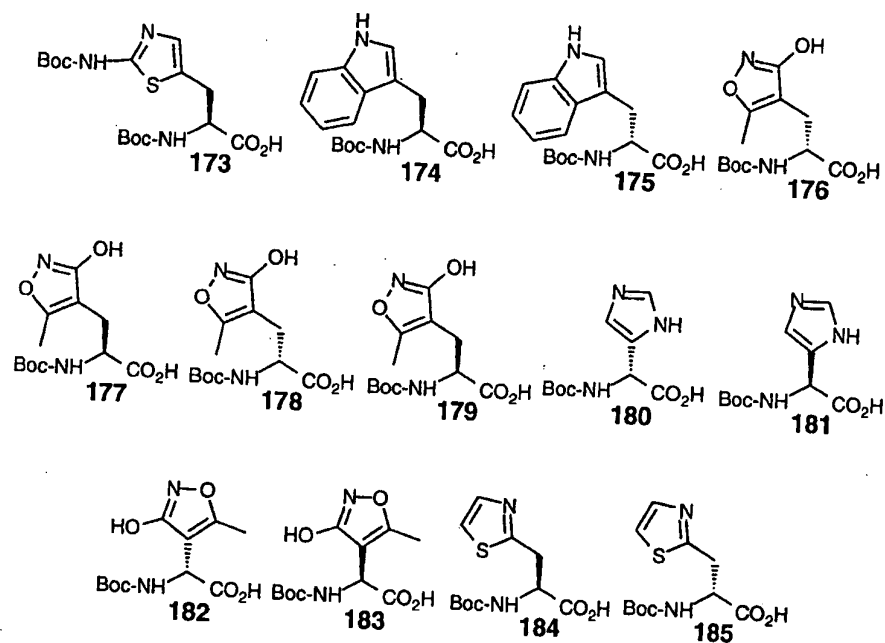
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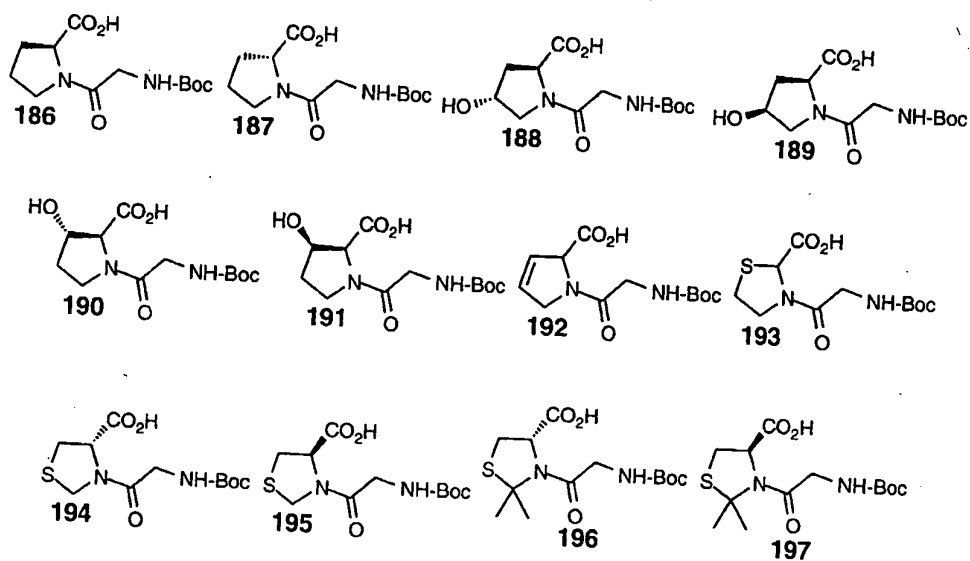
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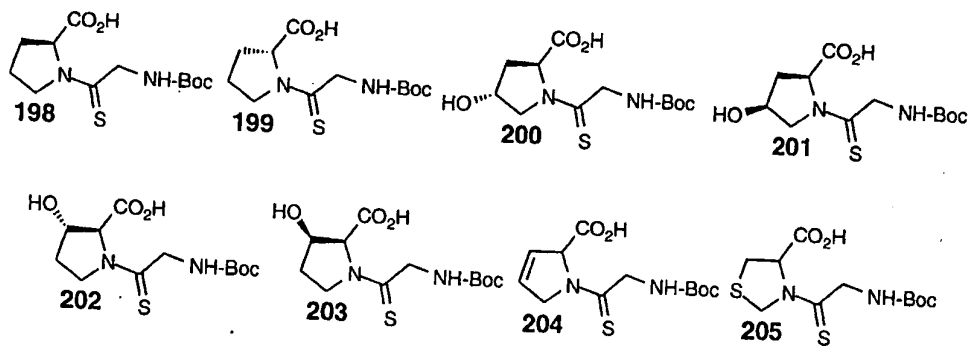
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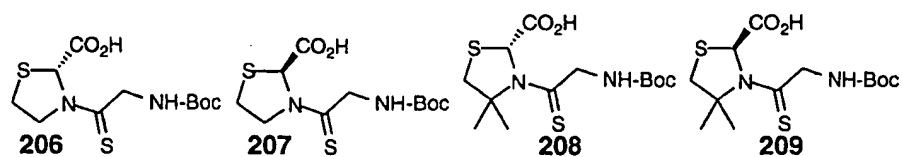


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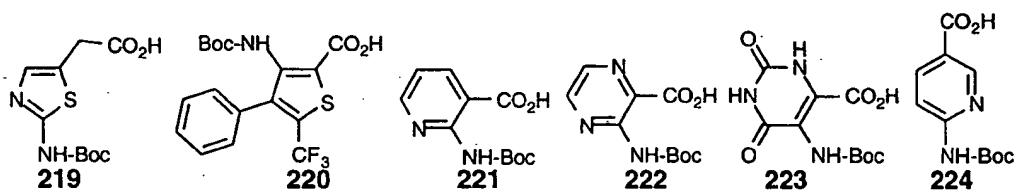
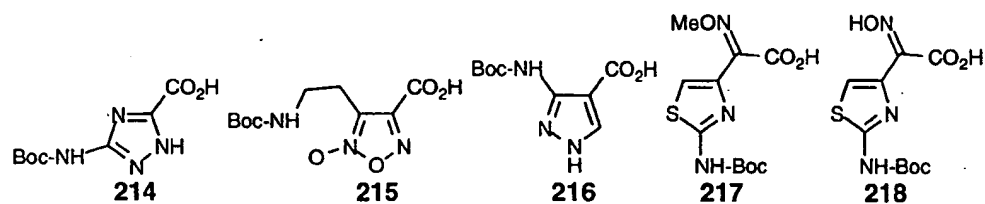
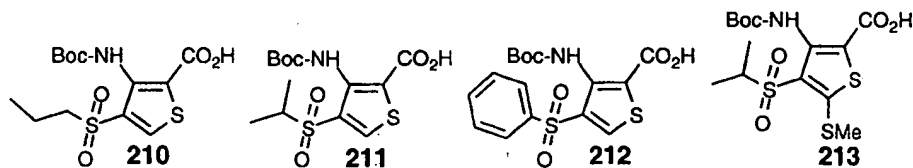


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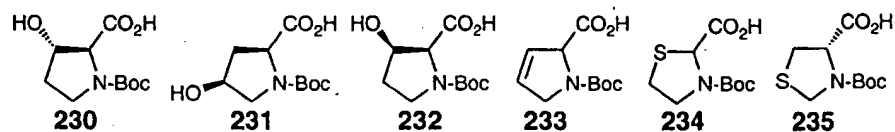
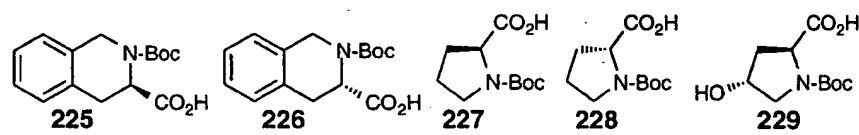




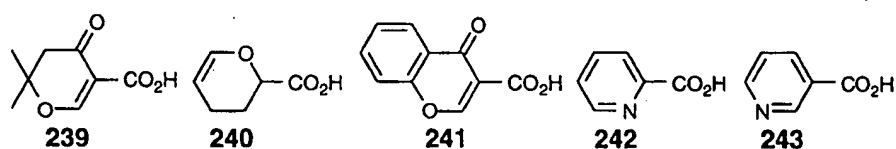
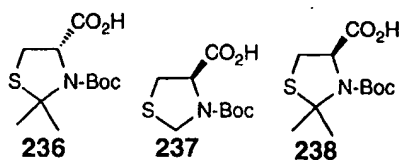
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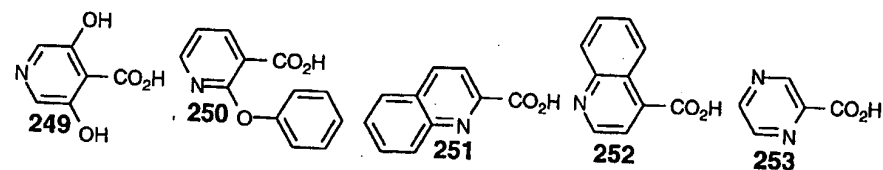
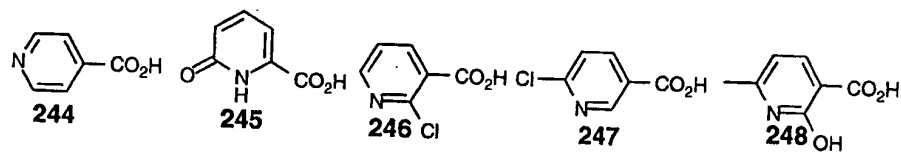
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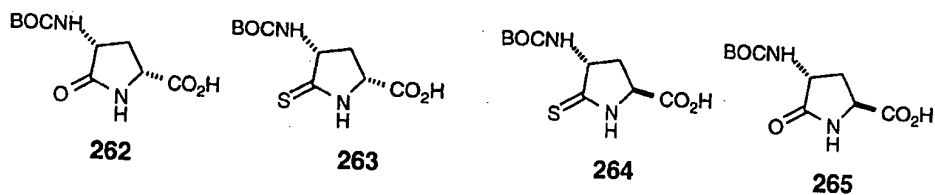
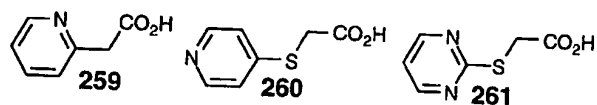
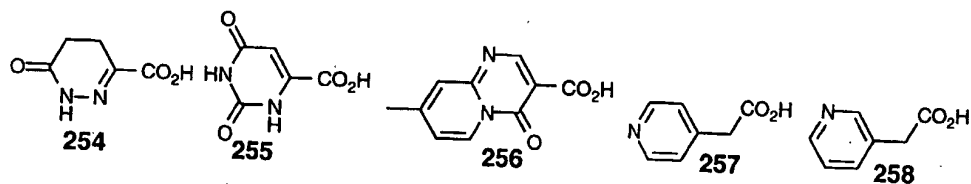
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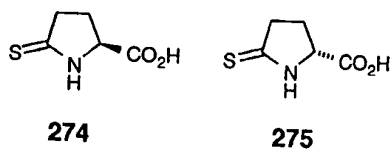
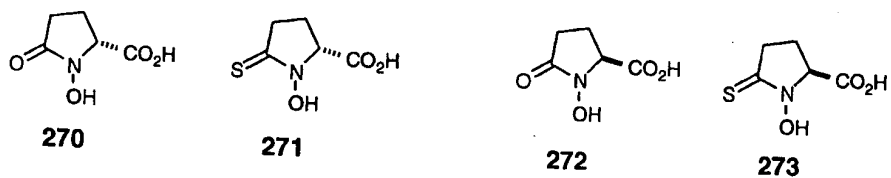
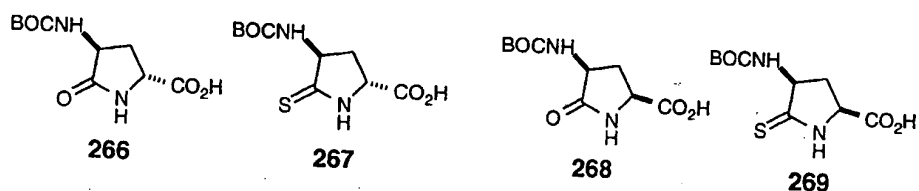
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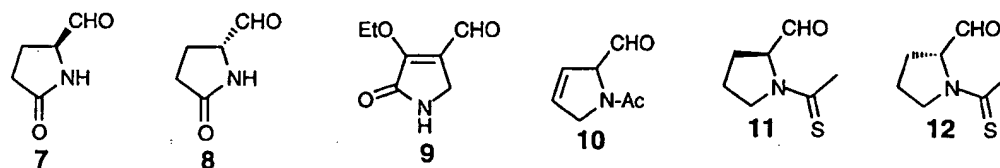
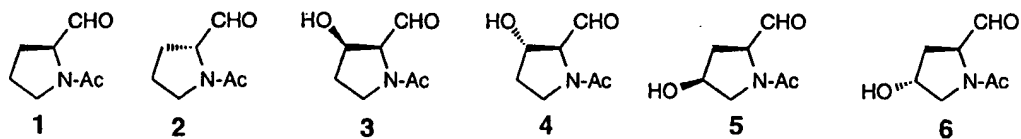


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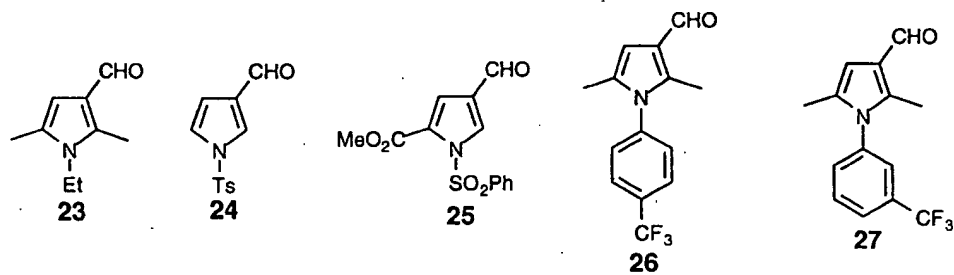
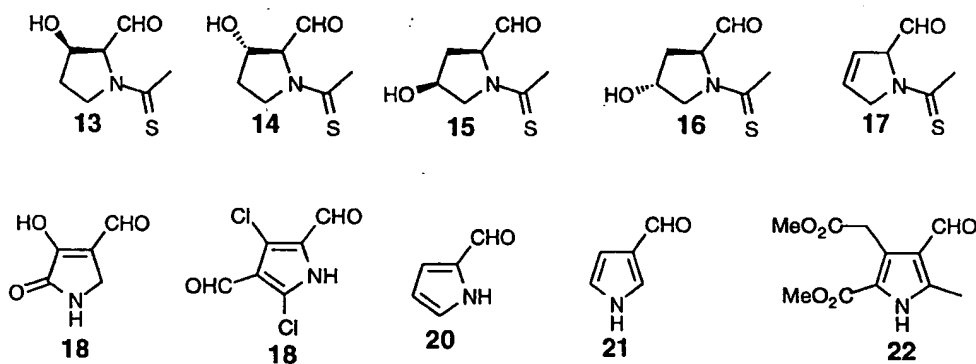


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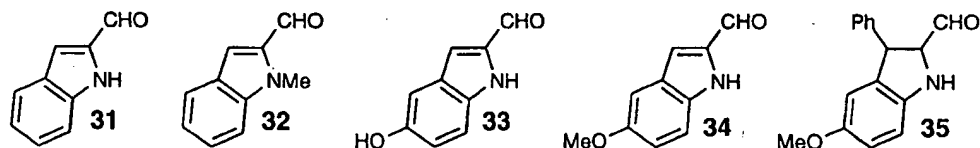
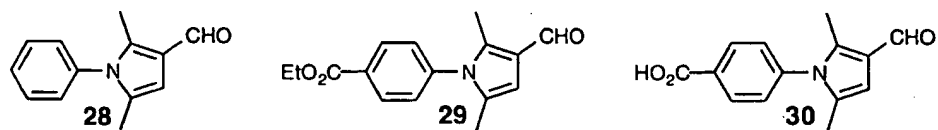
Table 14. Aldehydes of the type A-CHO



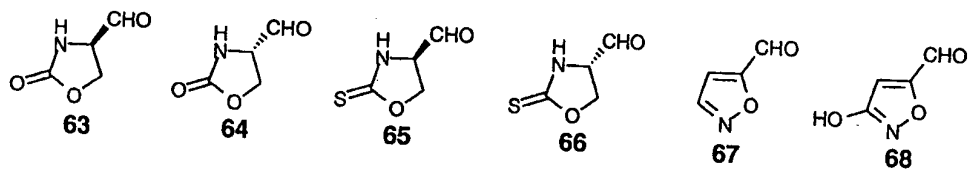
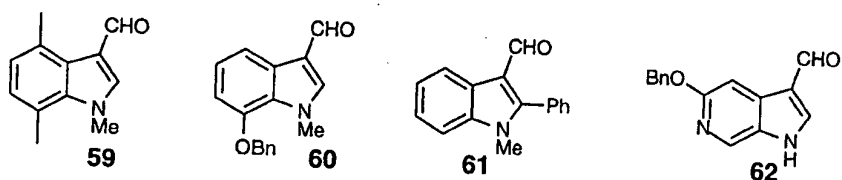
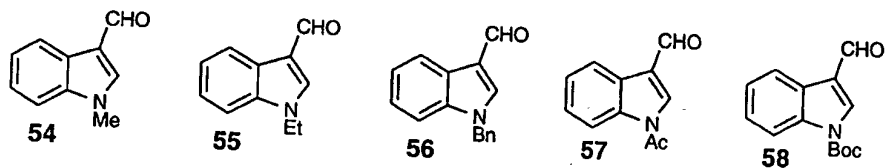
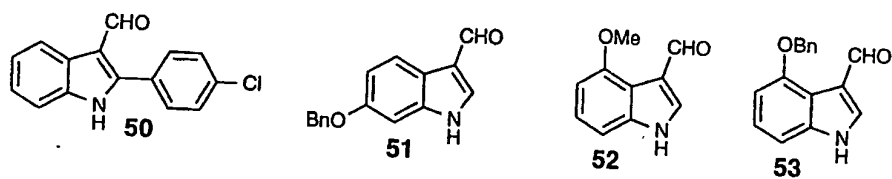
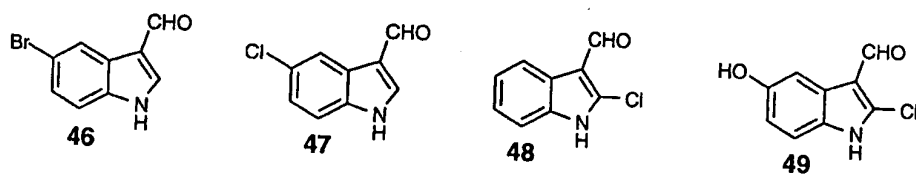
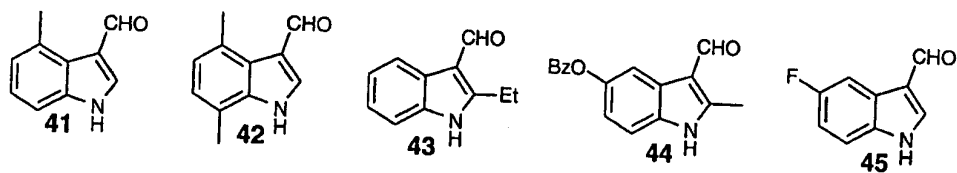
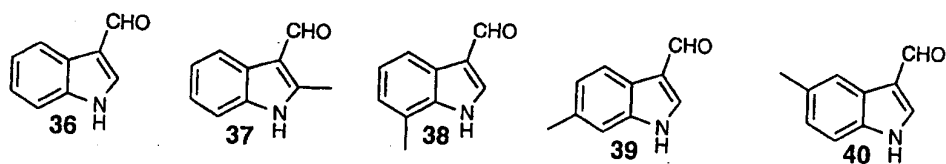
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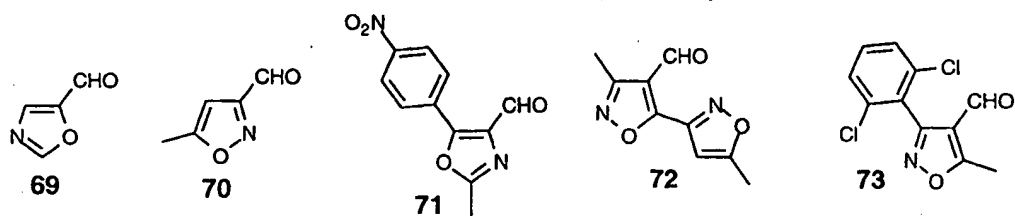


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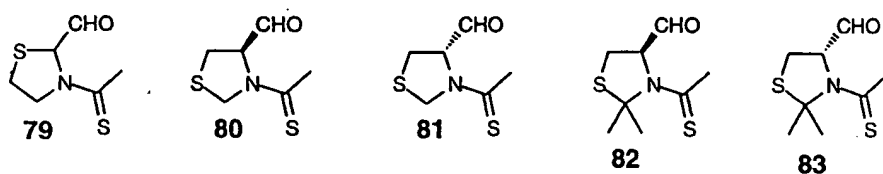
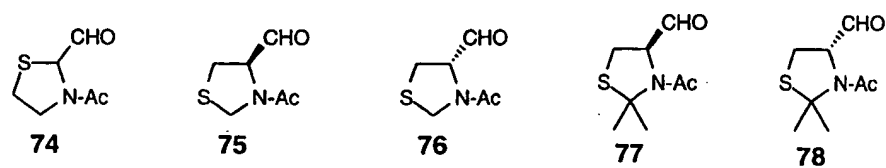


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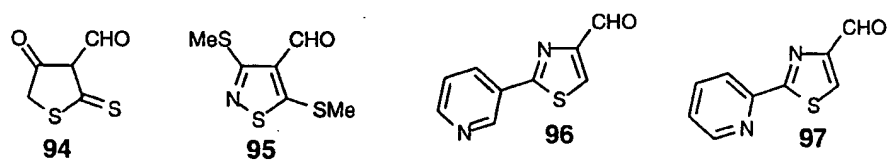
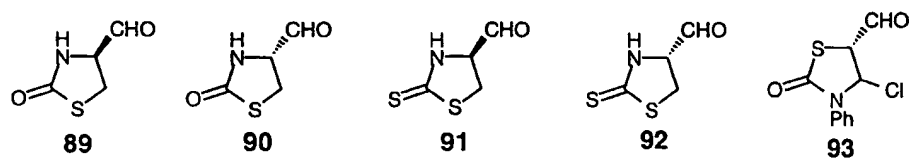
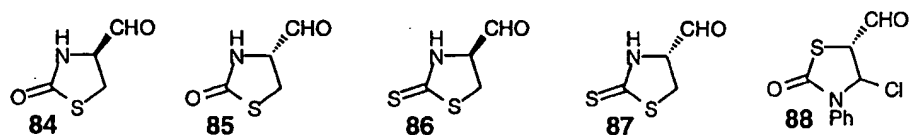




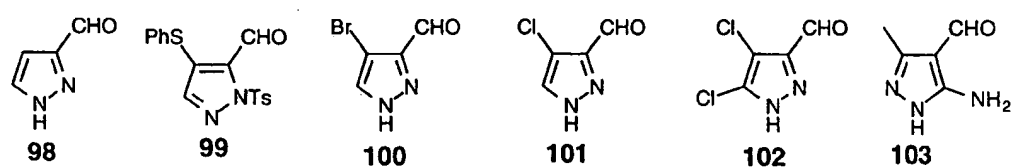
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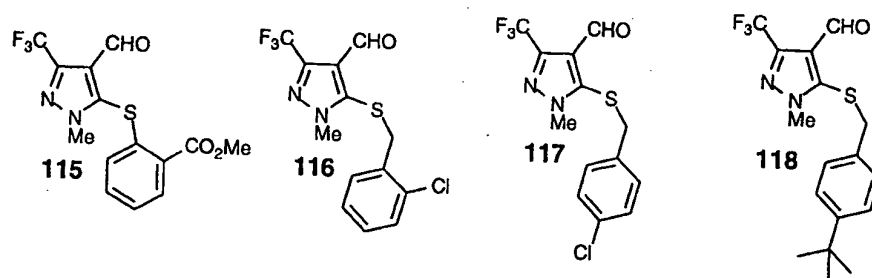
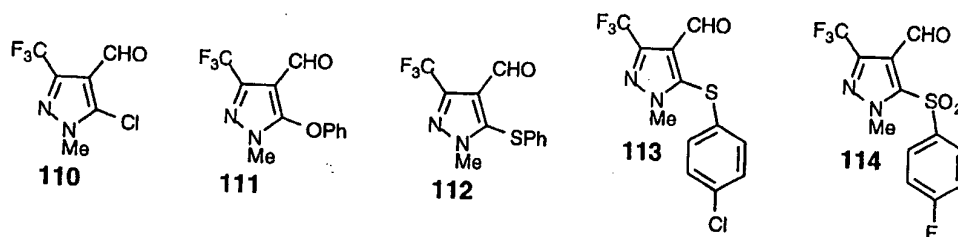
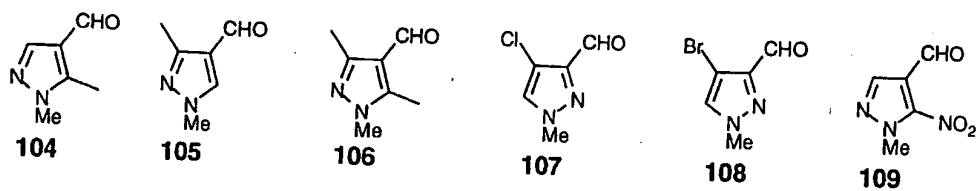
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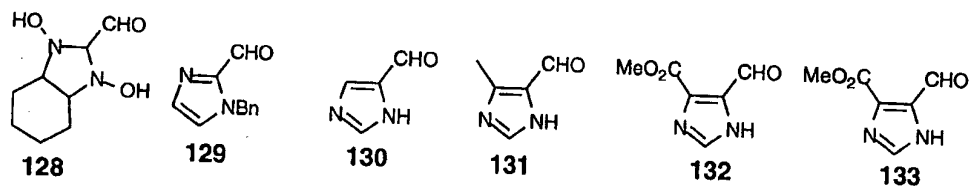
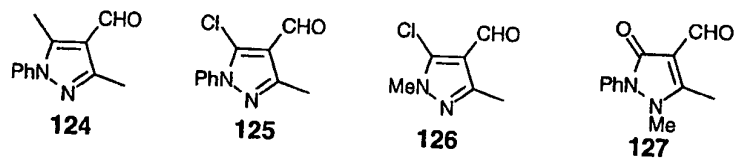
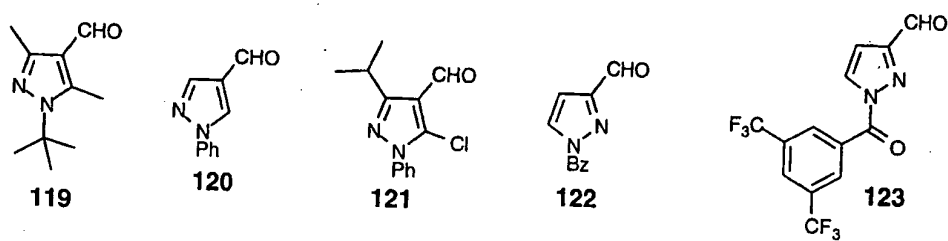
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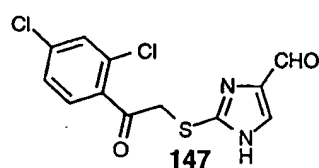
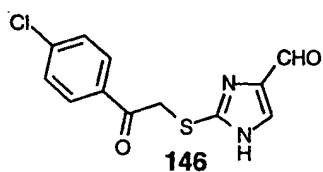
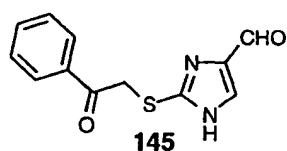
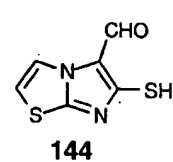
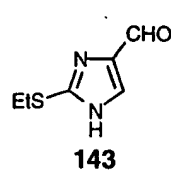
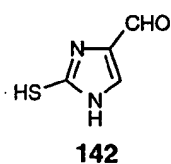
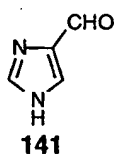
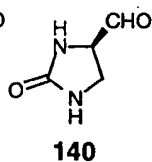
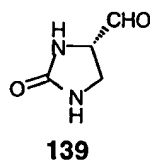
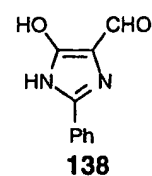
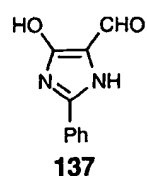
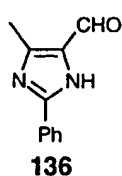
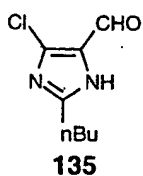
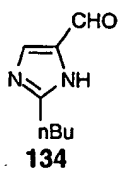
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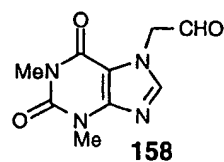
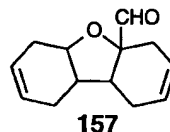
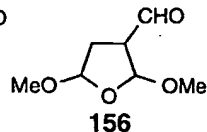
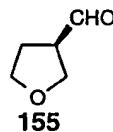
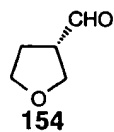
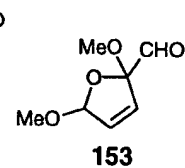
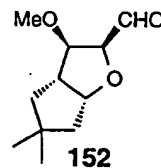
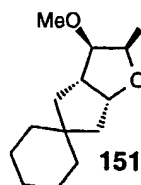
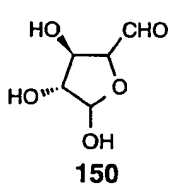
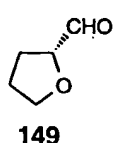
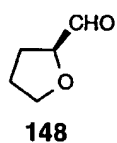
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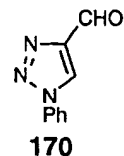
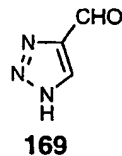
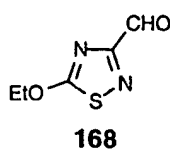
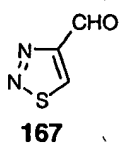
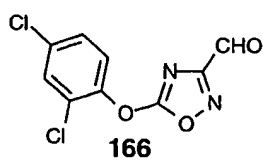
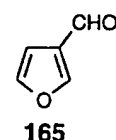
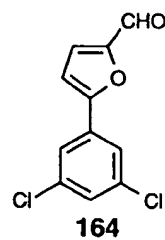
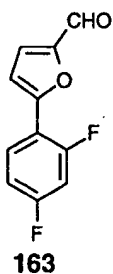
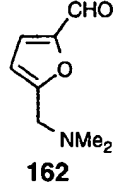
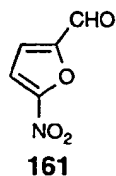
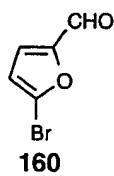
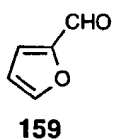
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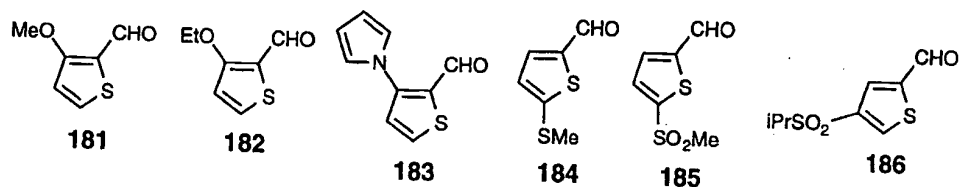
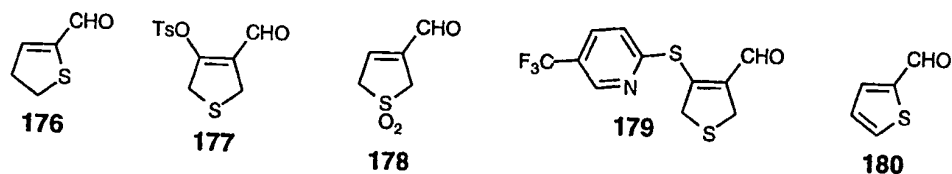
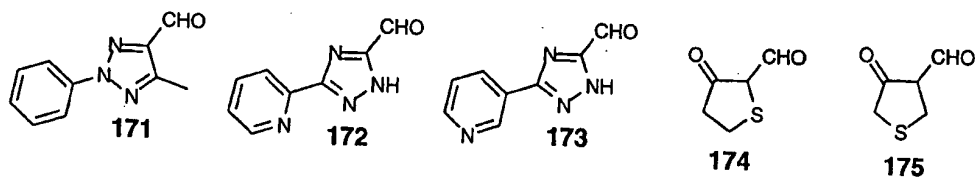
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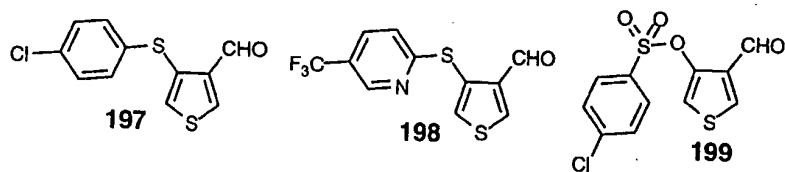
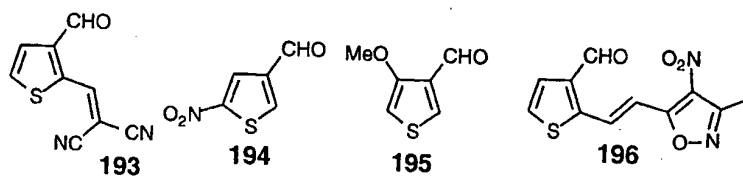
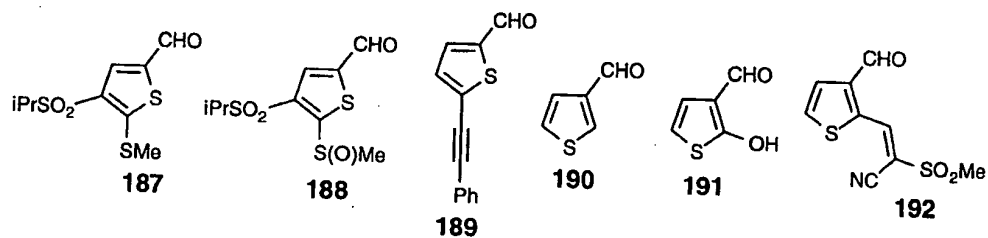
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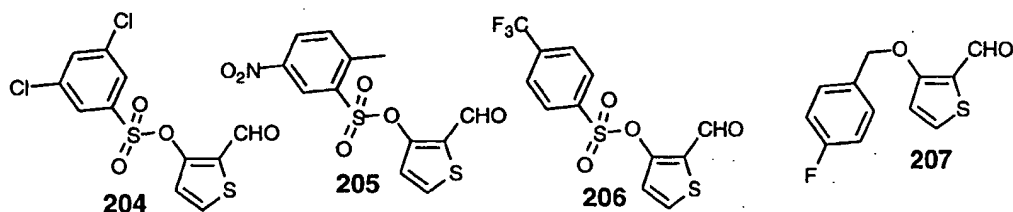
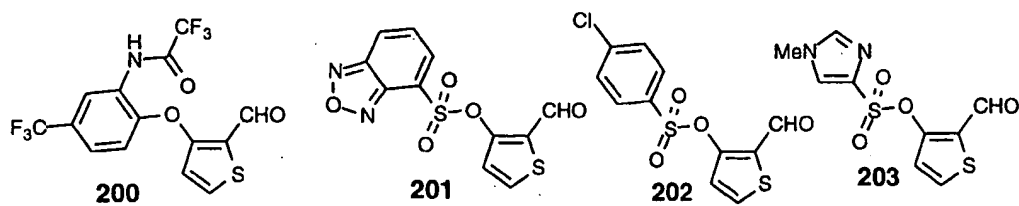
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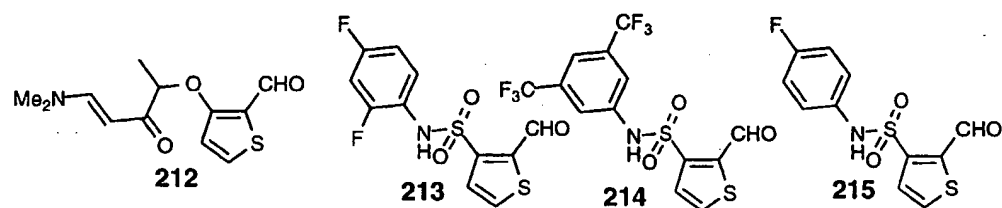
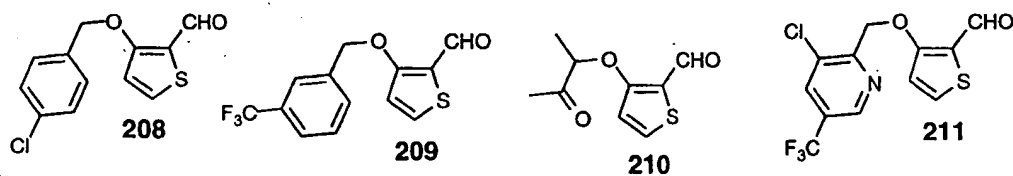
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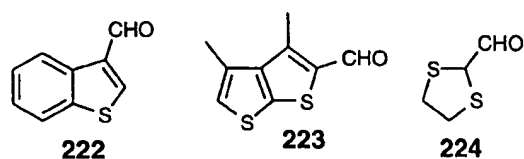
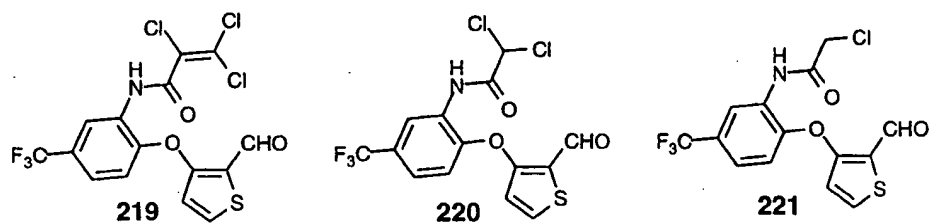
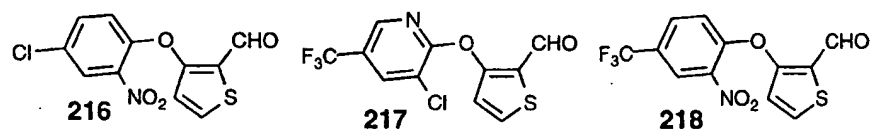
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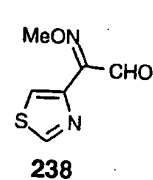
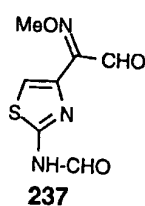
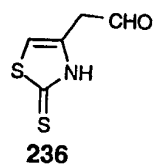
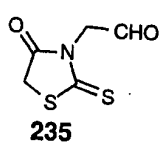
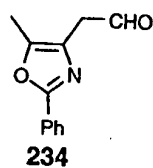
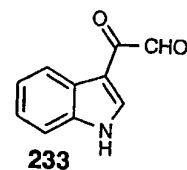
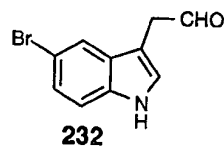
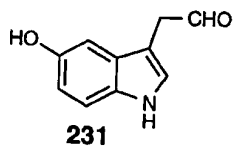
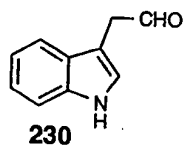
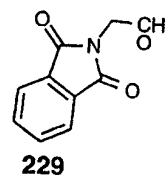
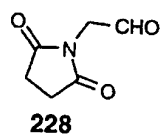
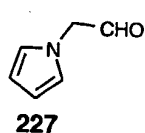
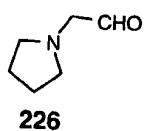
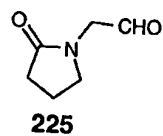
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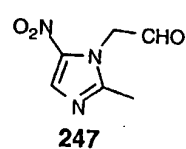
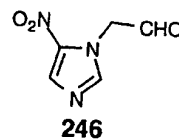
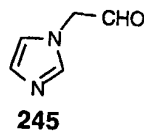
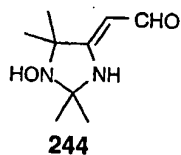
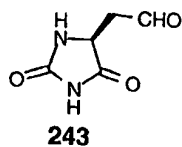
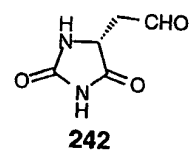
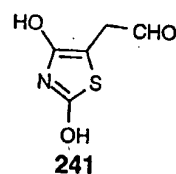
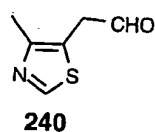
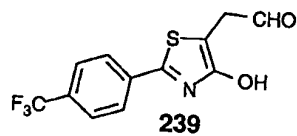
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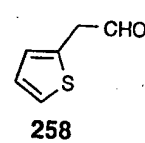
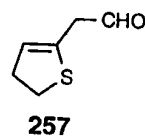
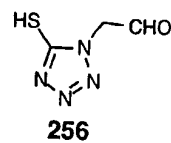
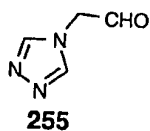
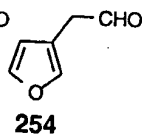
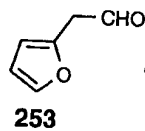
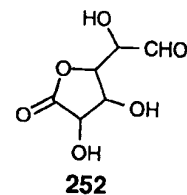
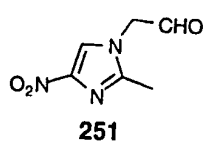
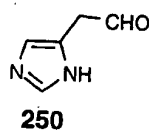
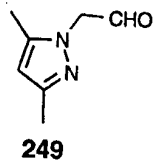
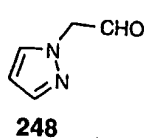
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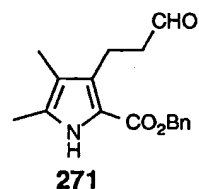
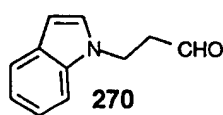
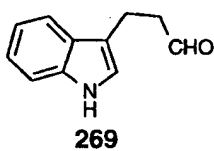
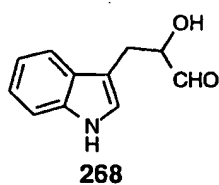
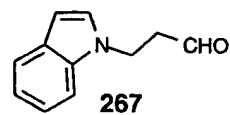
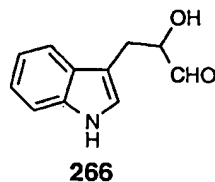
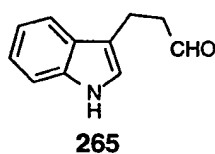
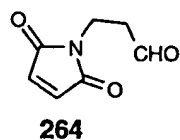
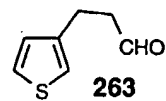
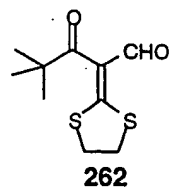
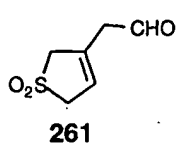
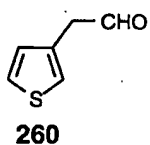
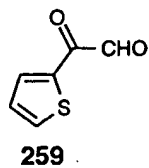
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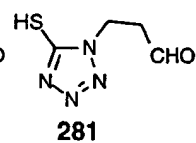
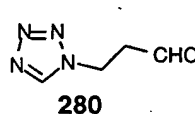
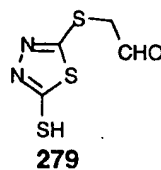
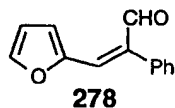
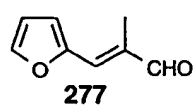
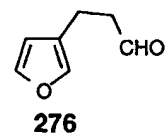
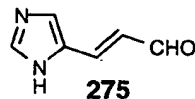
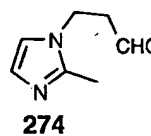
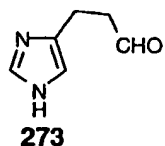
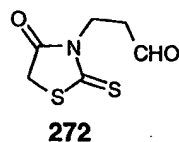
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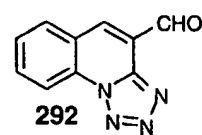
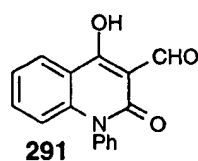
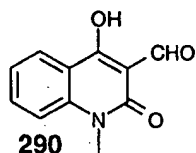
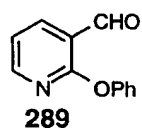
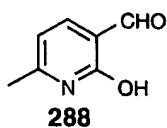
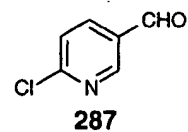
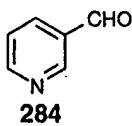
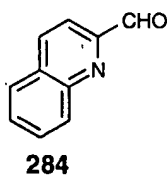
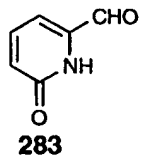
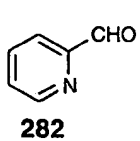
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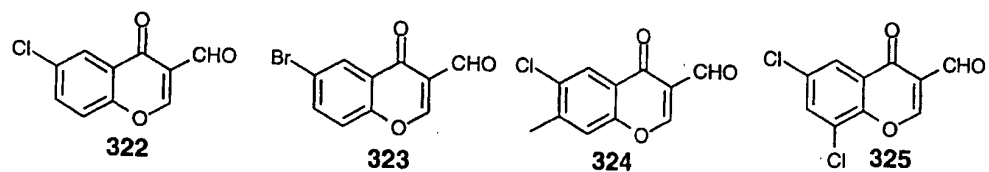
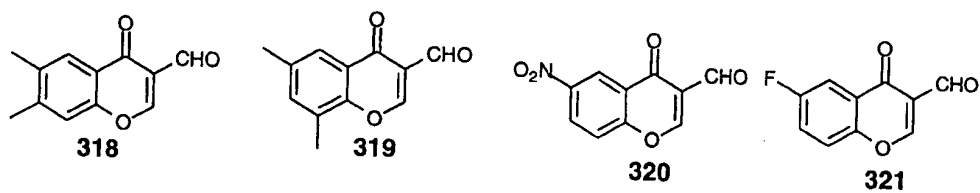
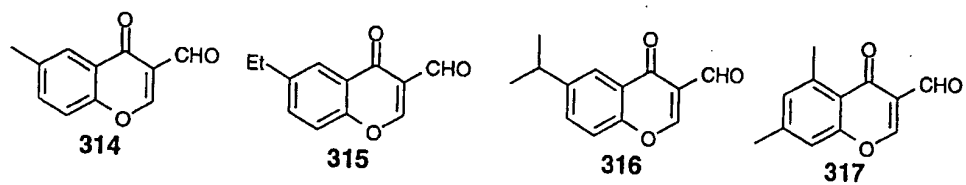
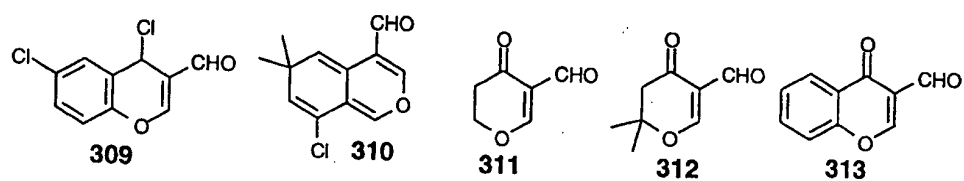
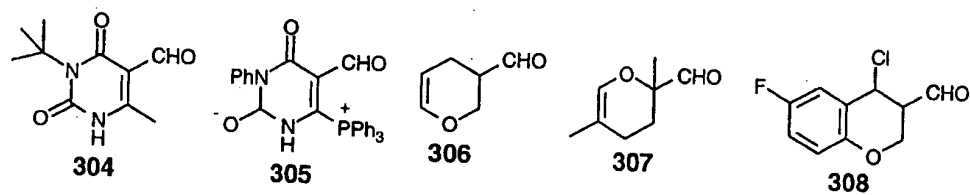
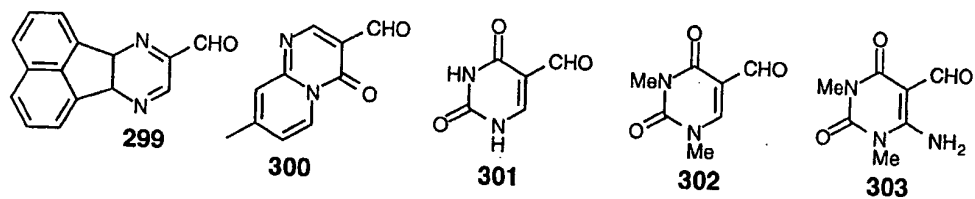
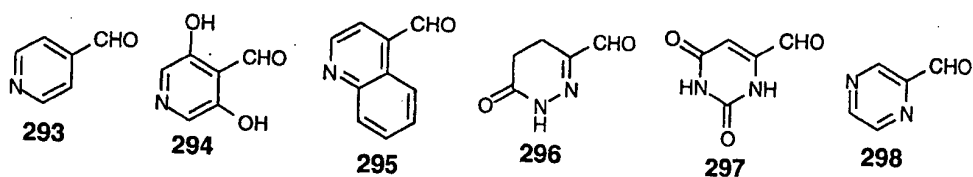


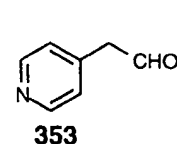
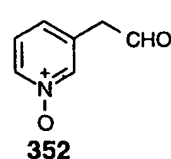
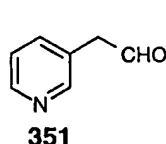
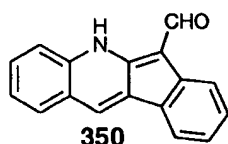
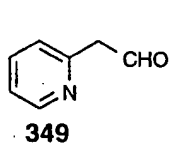
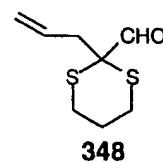
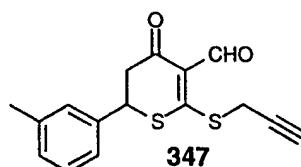
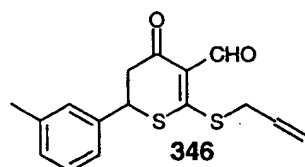
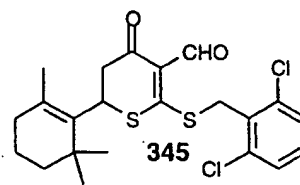
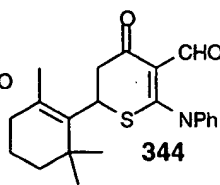
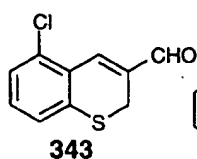
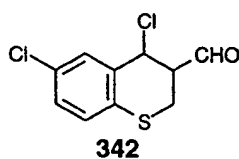
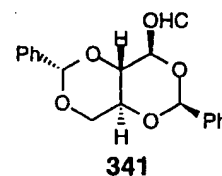
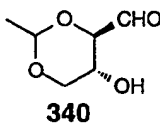
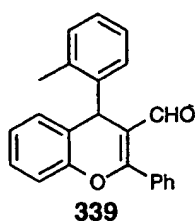
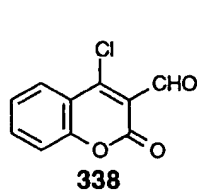
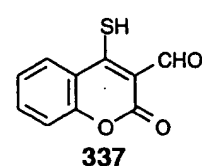
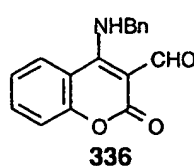
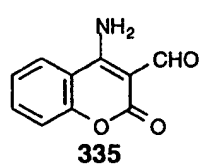
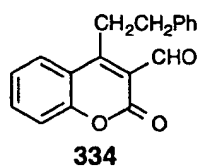
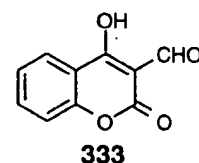
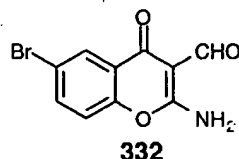
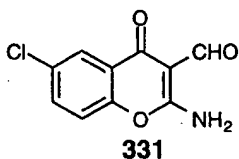
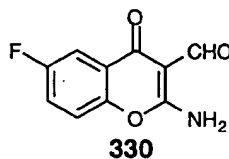
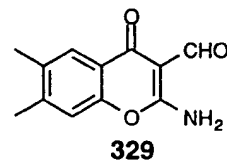
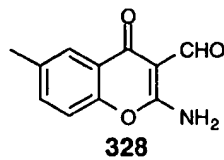
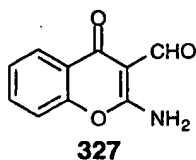
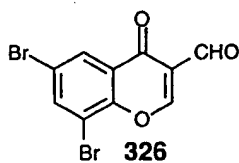
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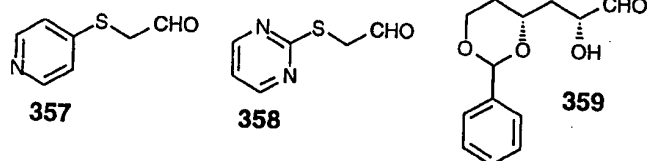
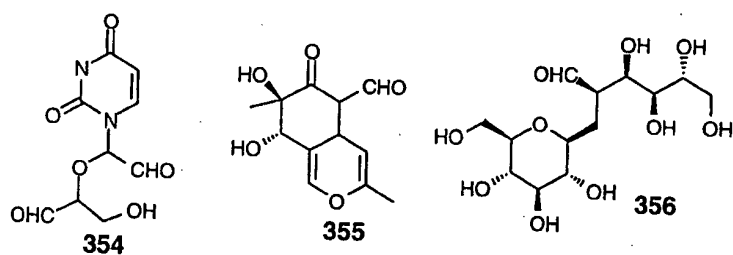




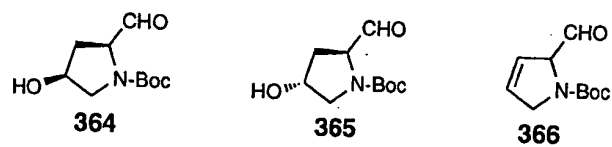
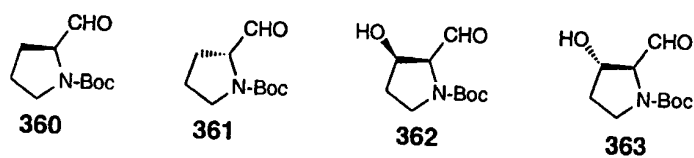
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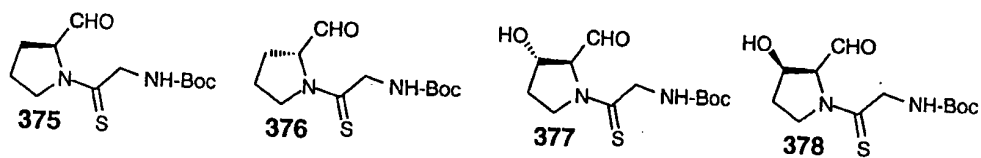
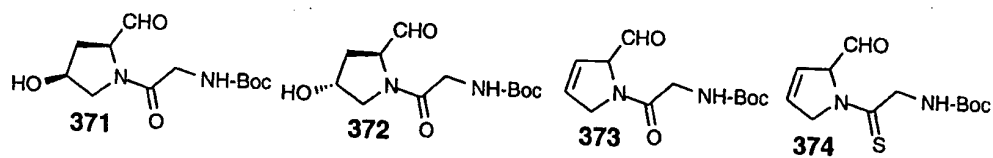
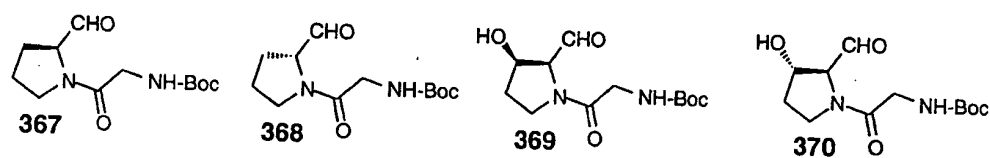
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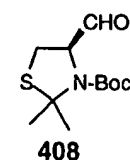
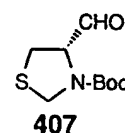
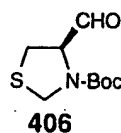
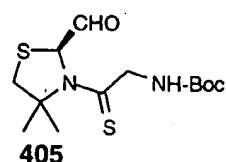
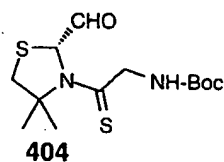
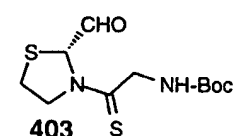
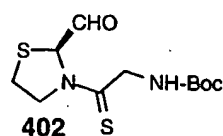
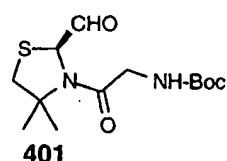
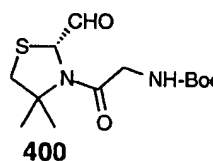
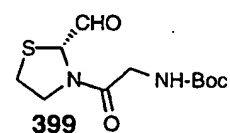
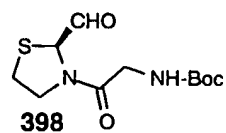
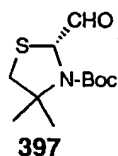
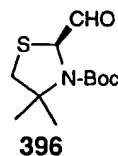
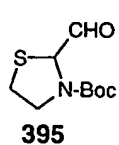
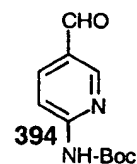
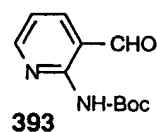
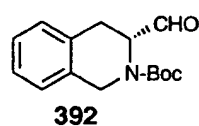
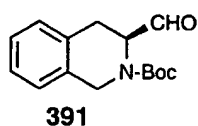
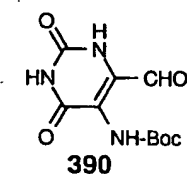
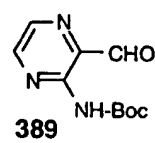
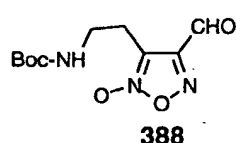
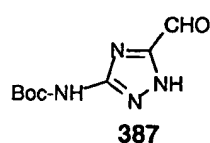
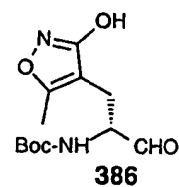
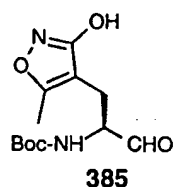
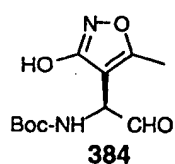
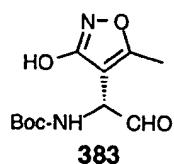
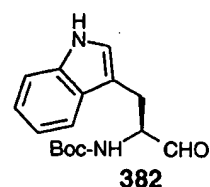
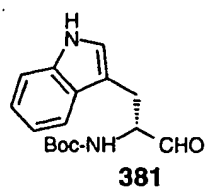
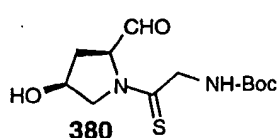
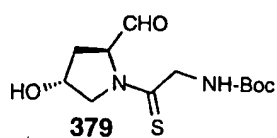
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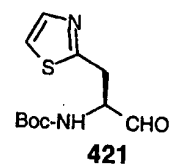
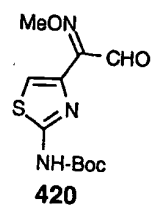
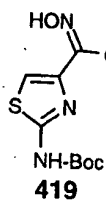
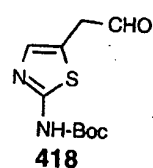
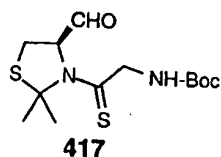
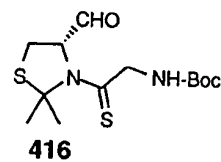
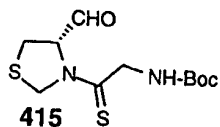
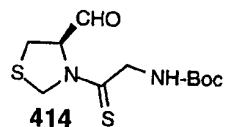
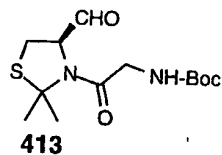
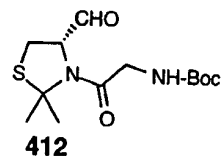
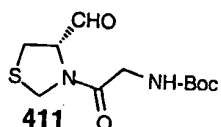
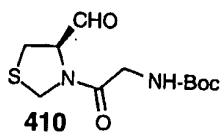
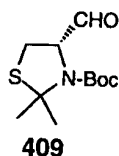
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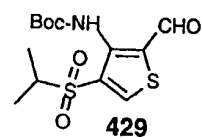
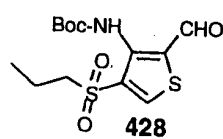
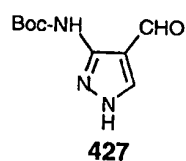
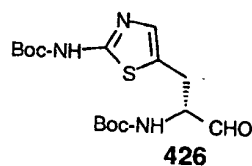
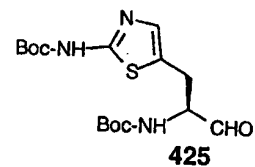
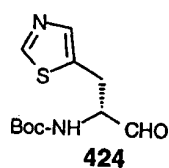
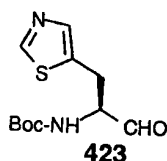
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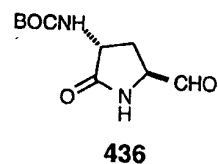
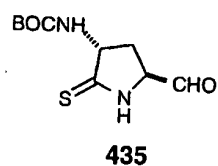
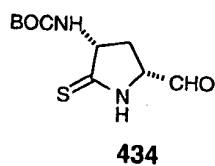
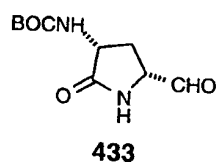
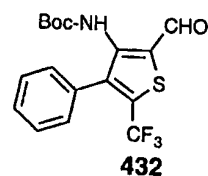
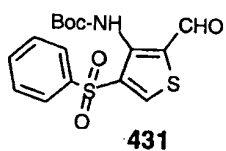
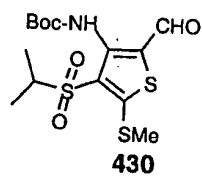
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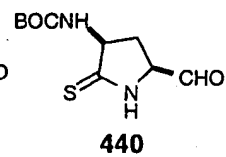
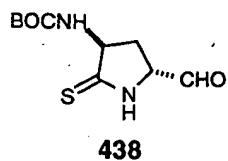
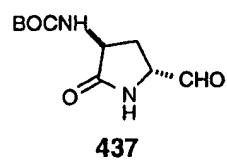


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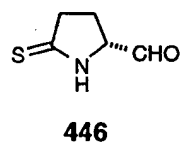
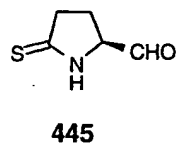
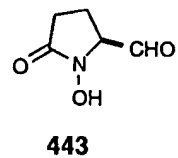
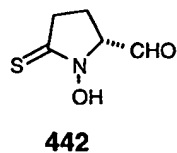
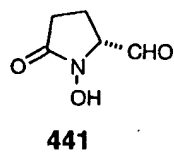
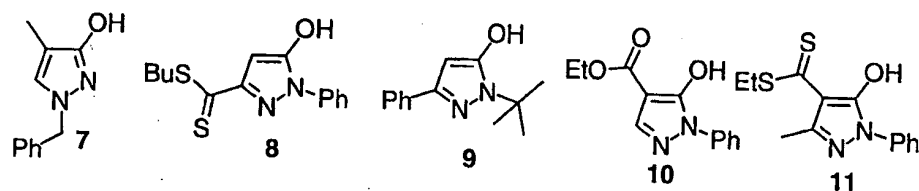
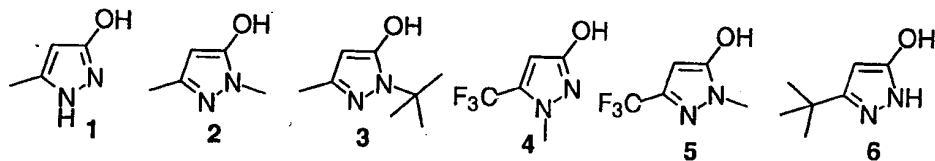
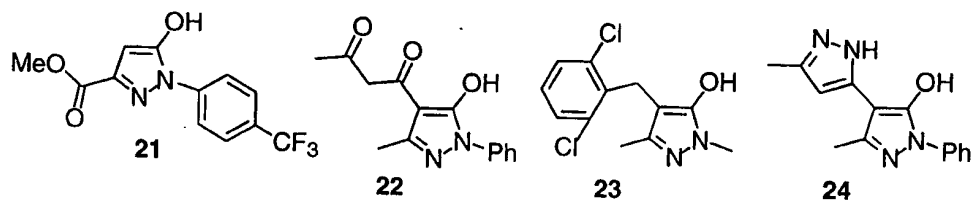
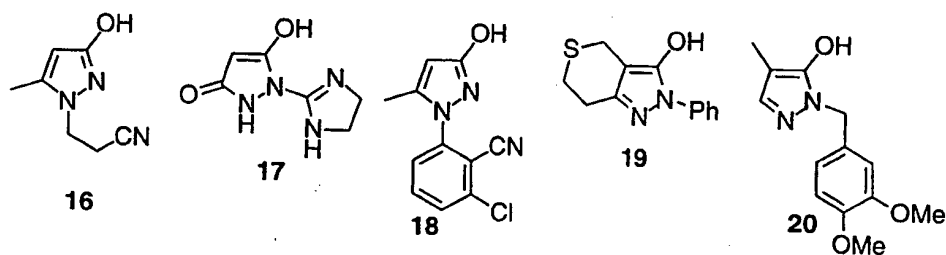
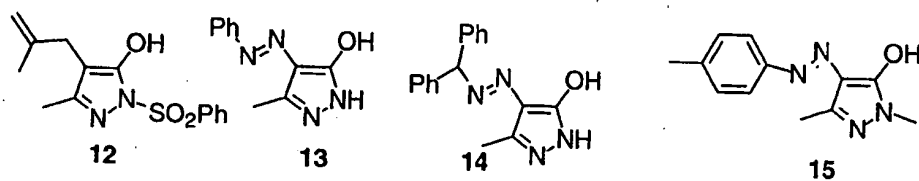


Table 15. Alcohols of the type A-OH

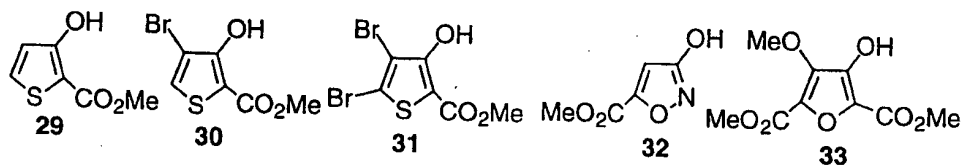
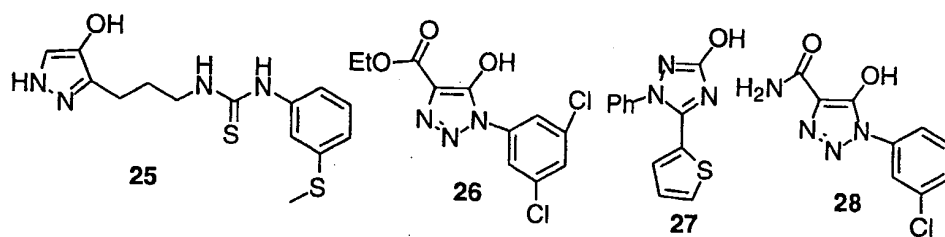
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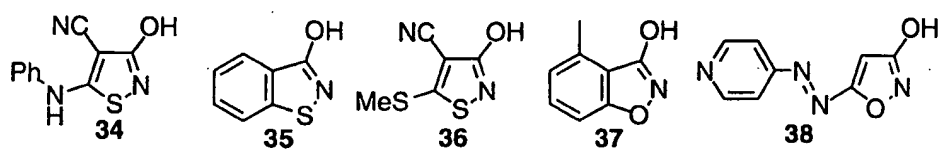


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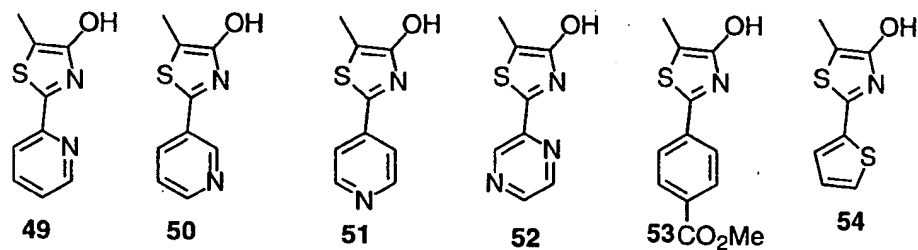
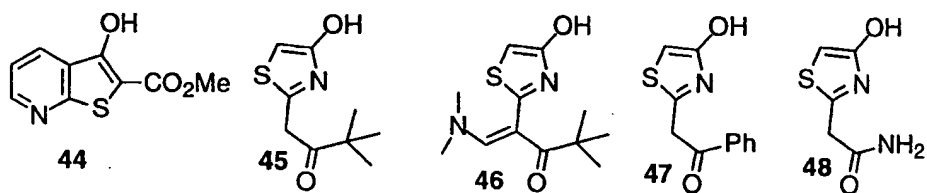
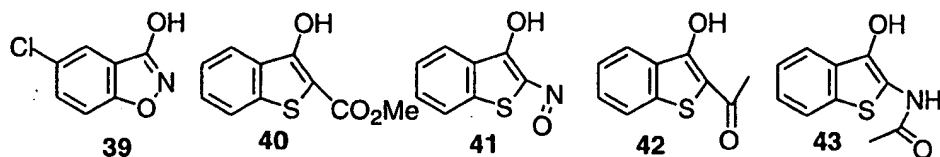


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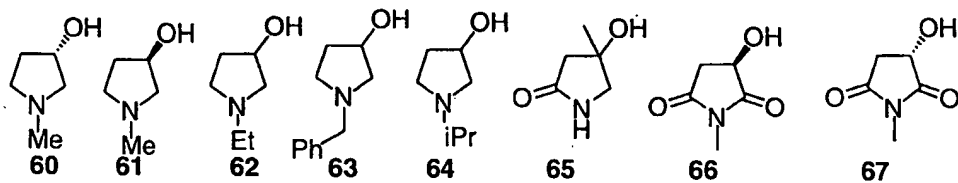
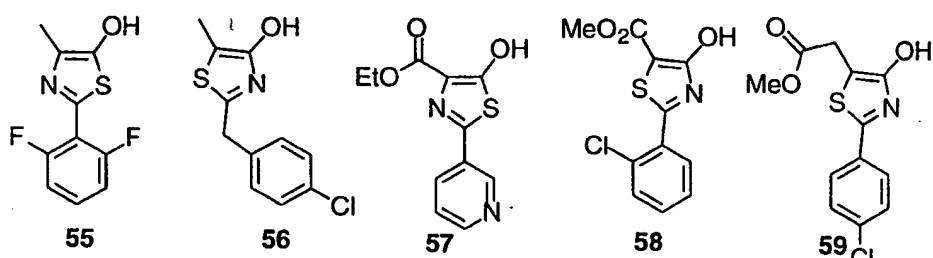




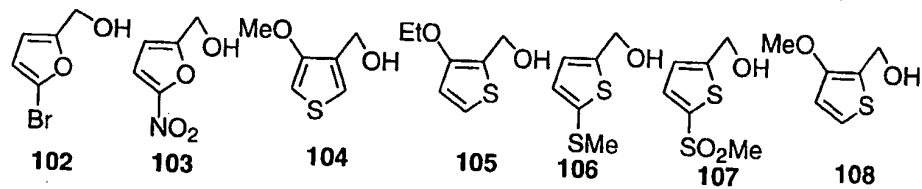
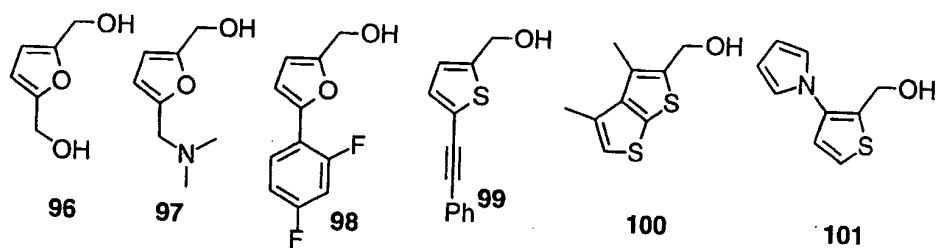
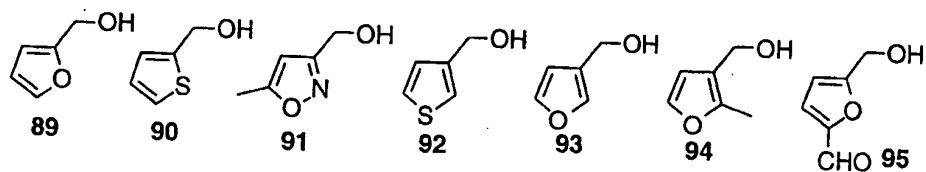
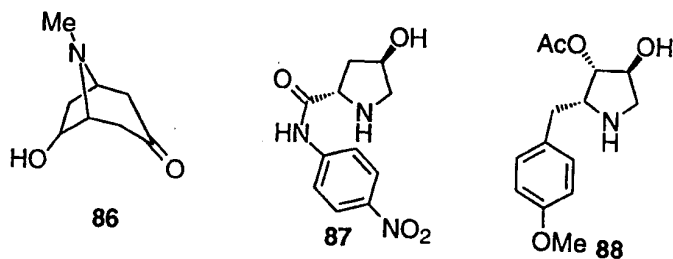
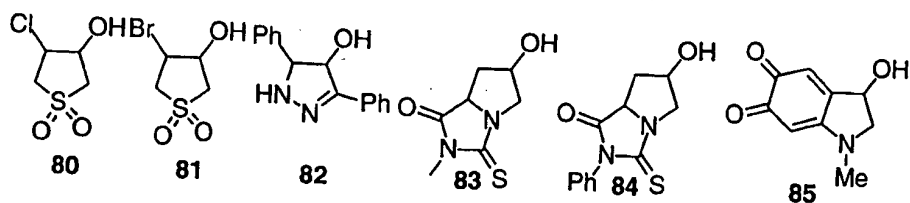
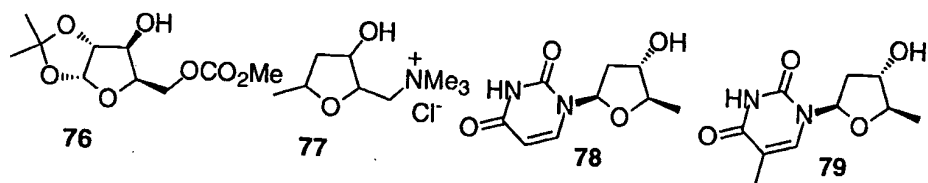
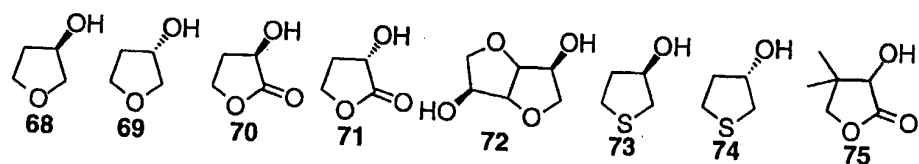
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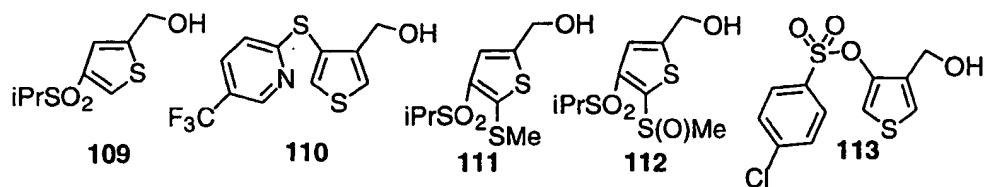


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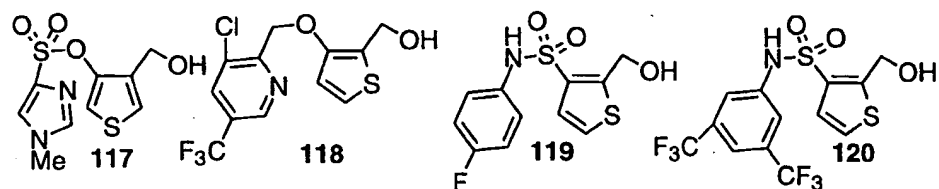
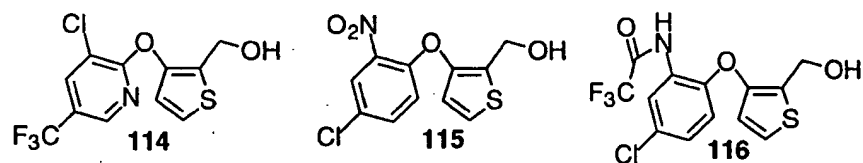


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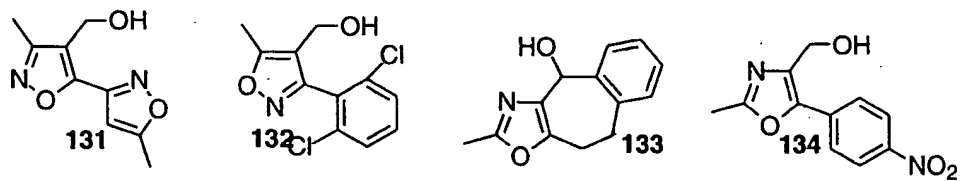
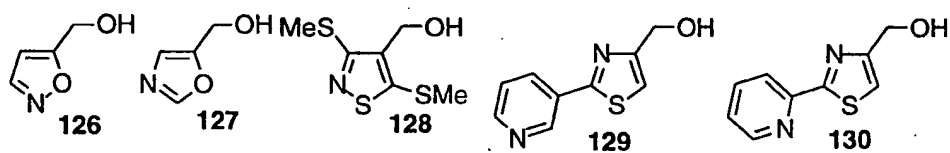
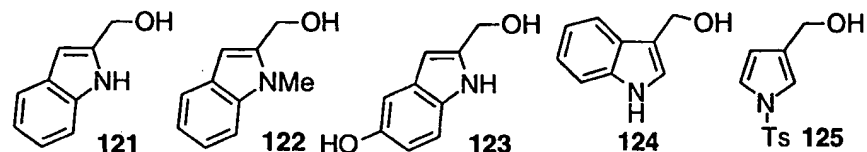
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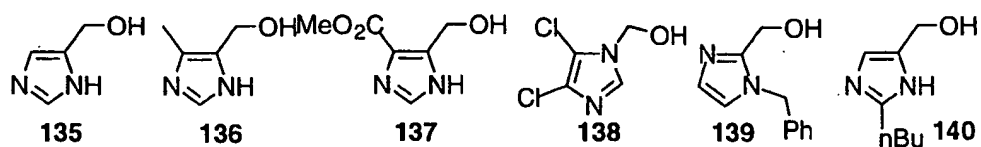
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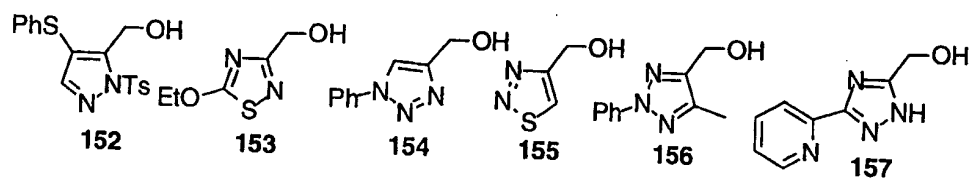
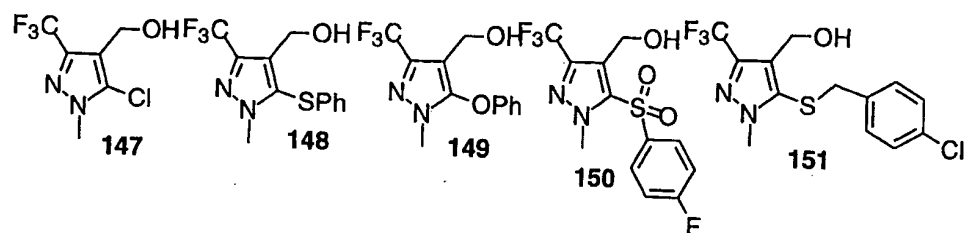
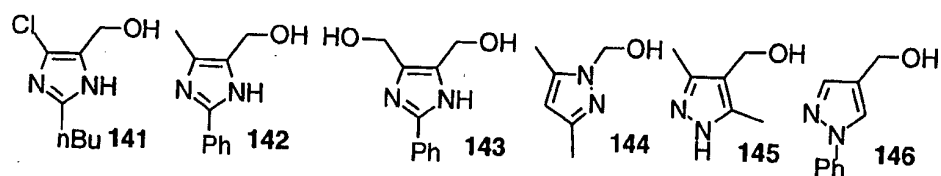
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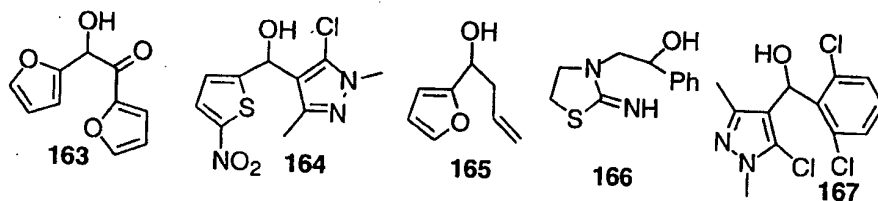
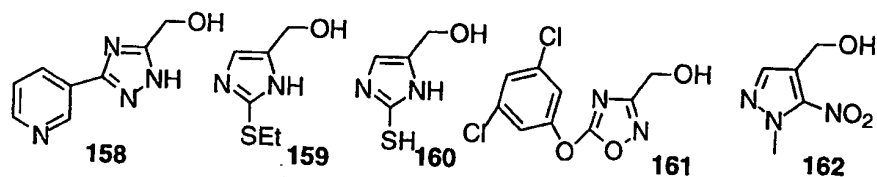
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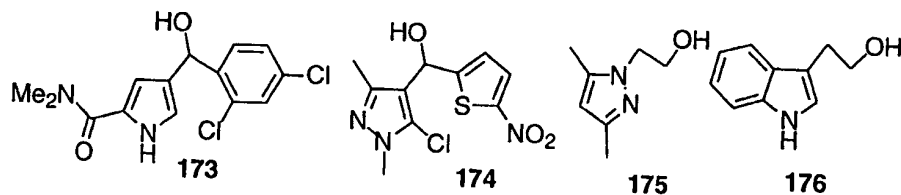
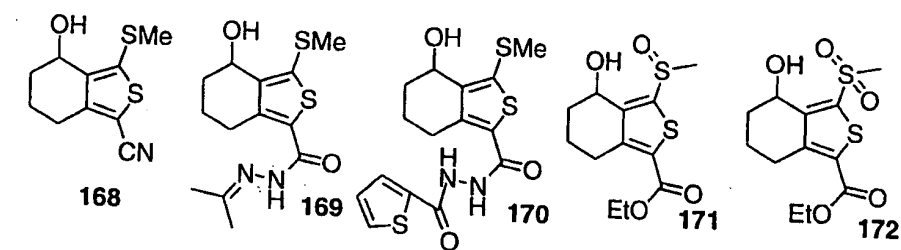
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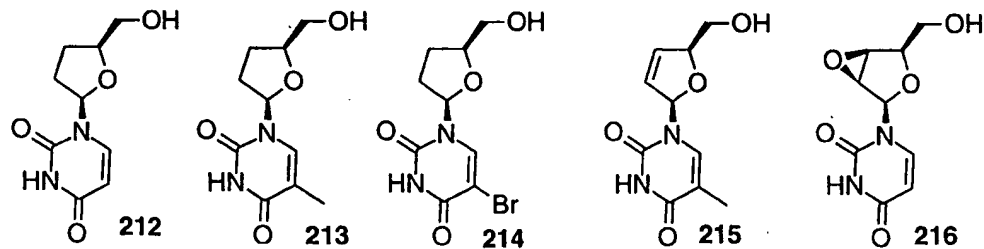
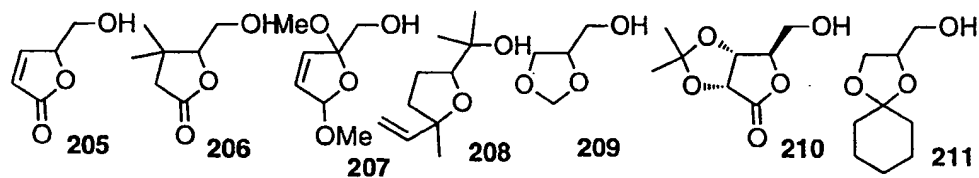
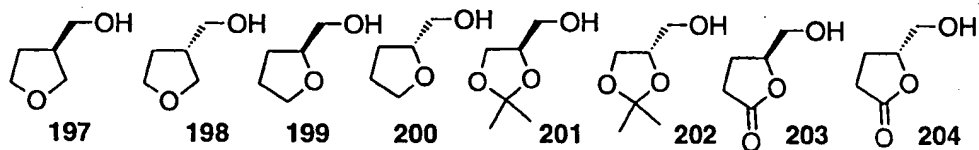
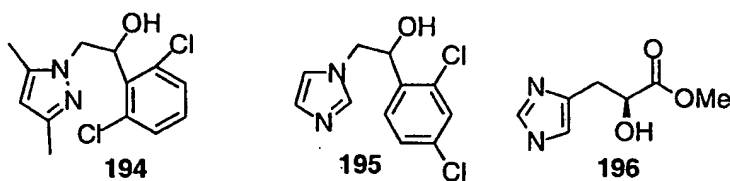
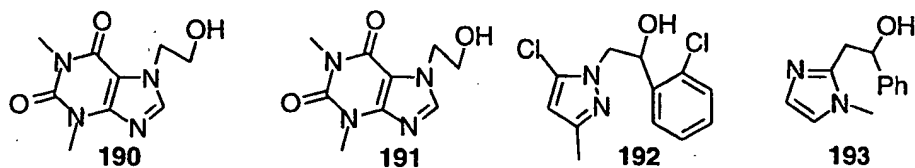
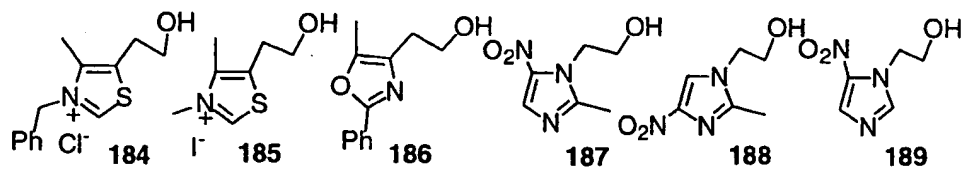
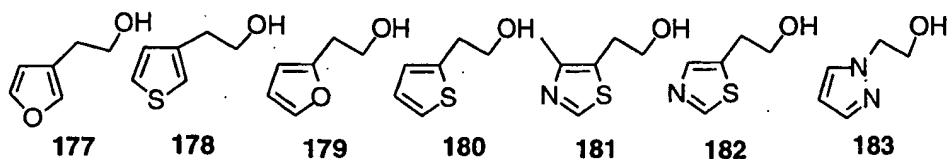


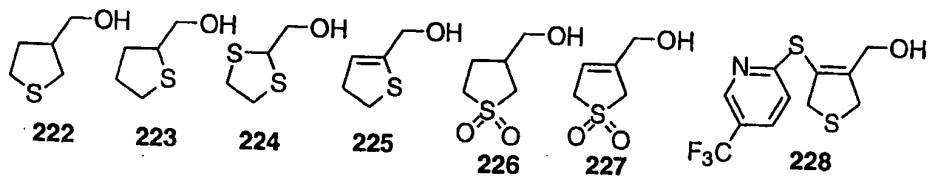
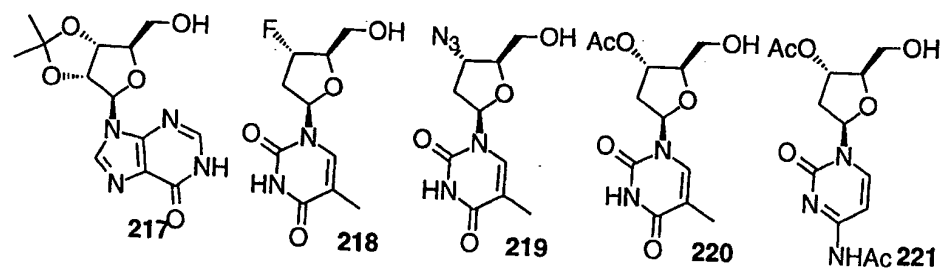
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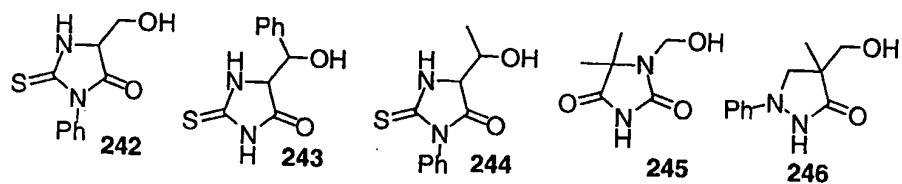
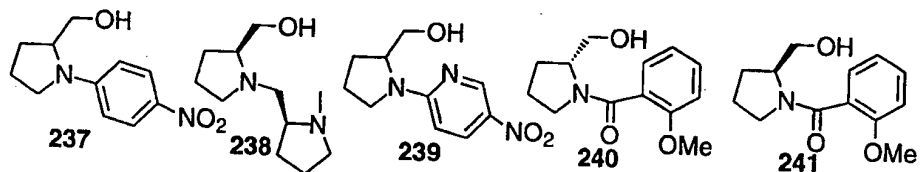
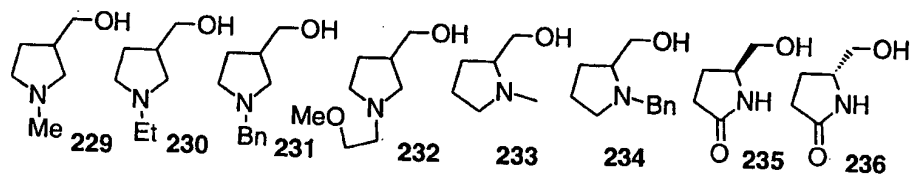
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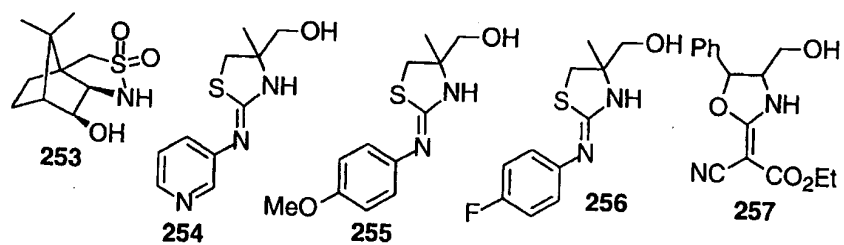
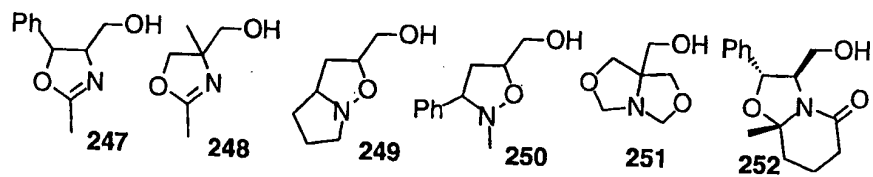




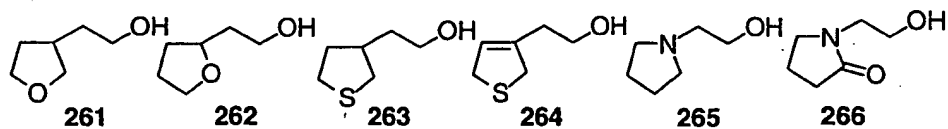
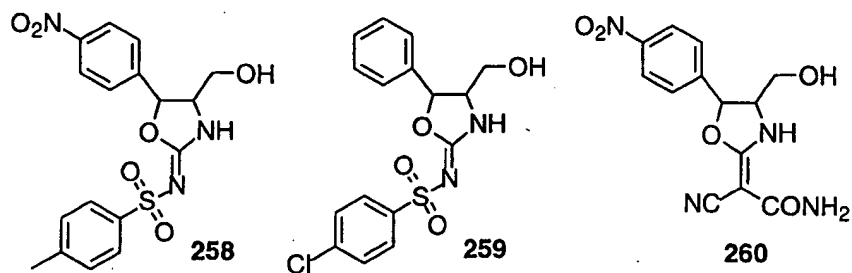
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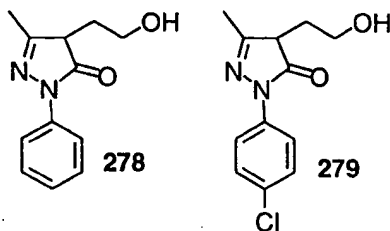
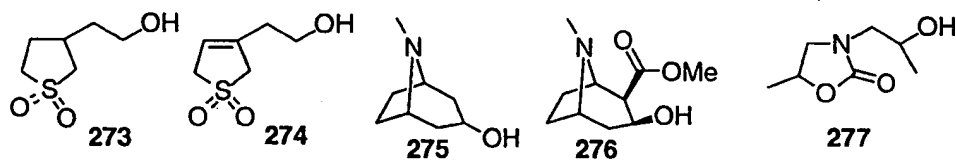
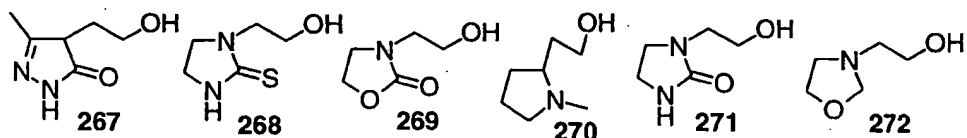
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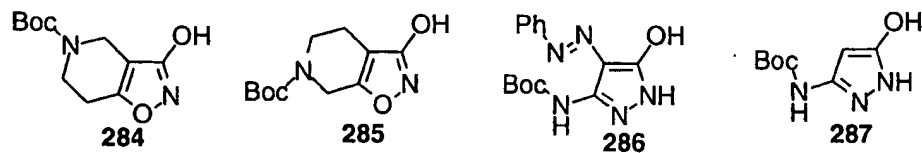
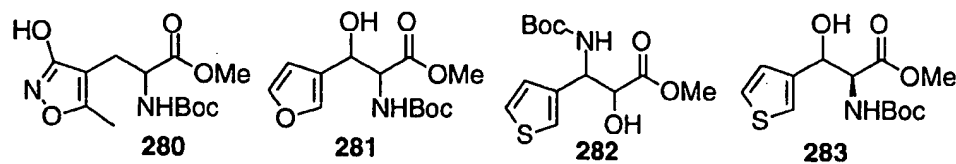
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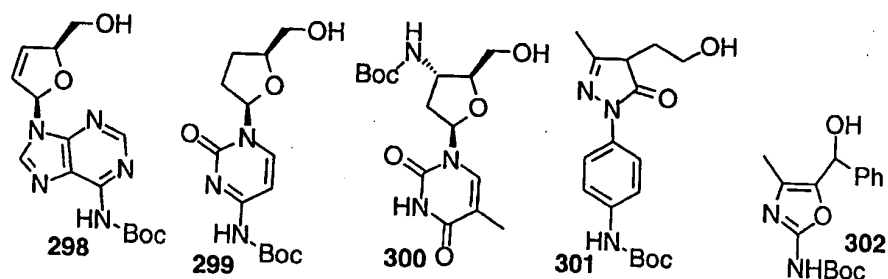
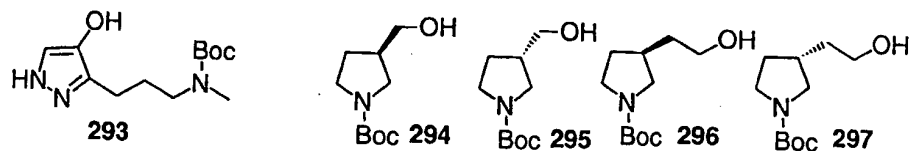
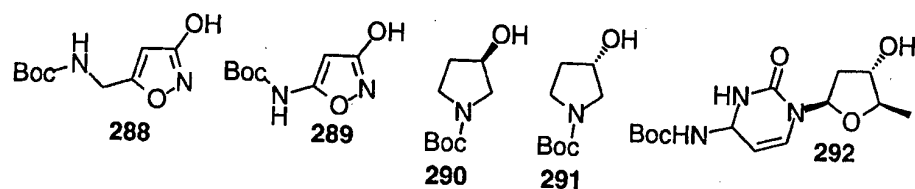
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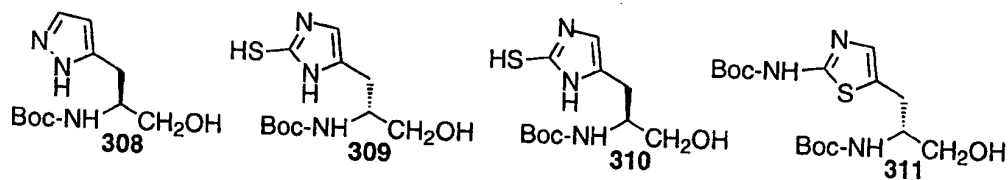
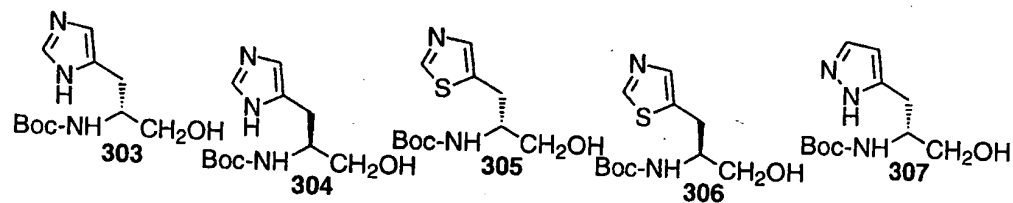
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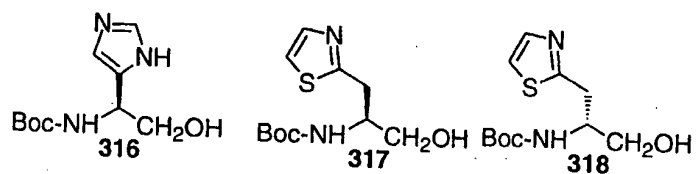
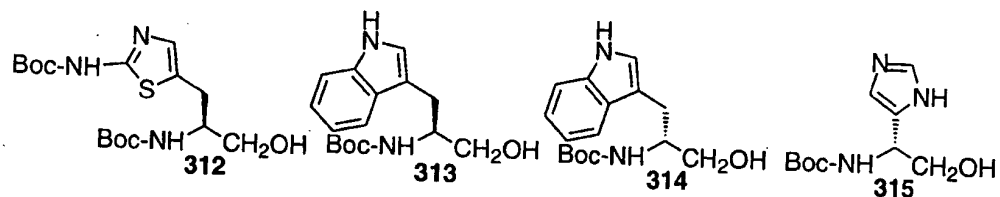
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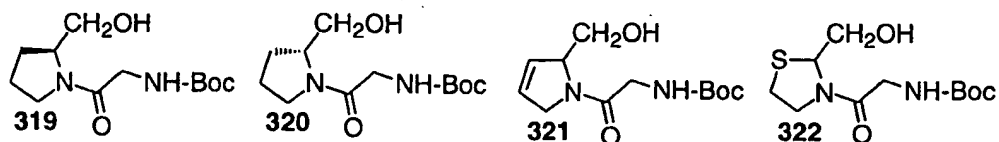


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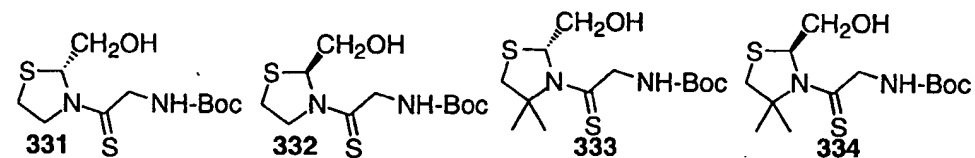
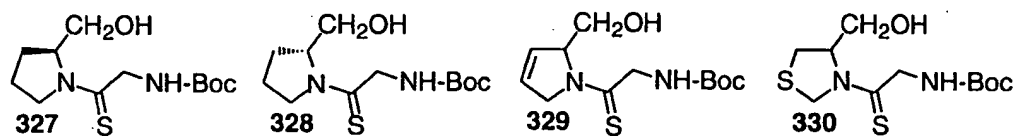
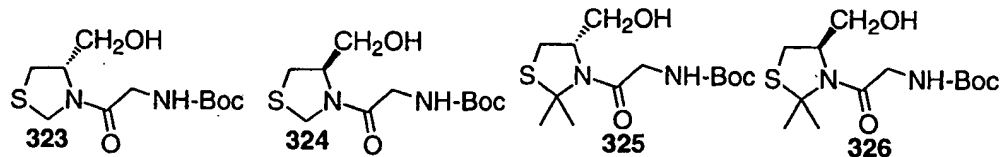


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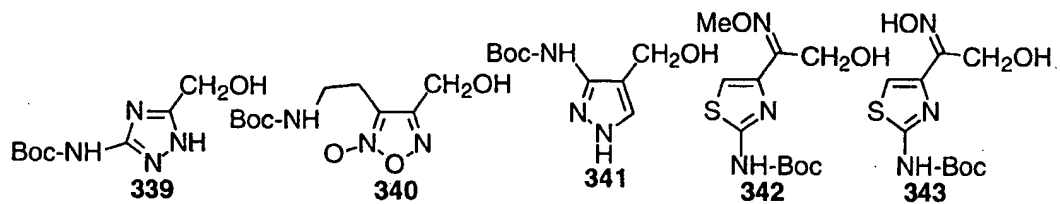
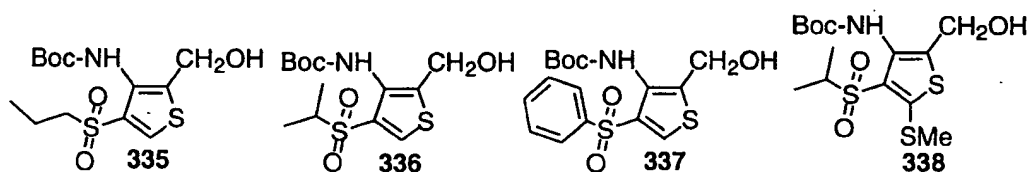




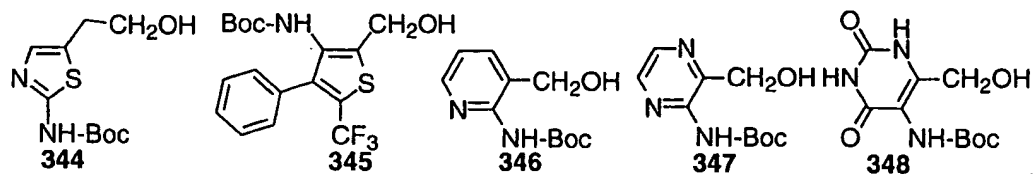
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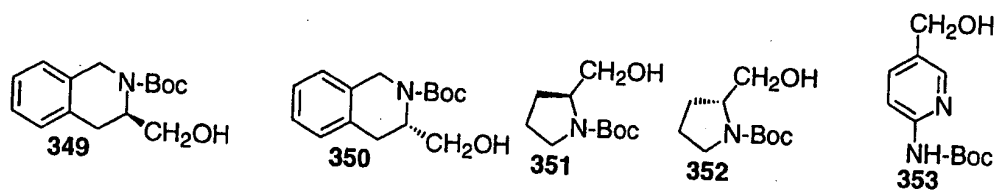


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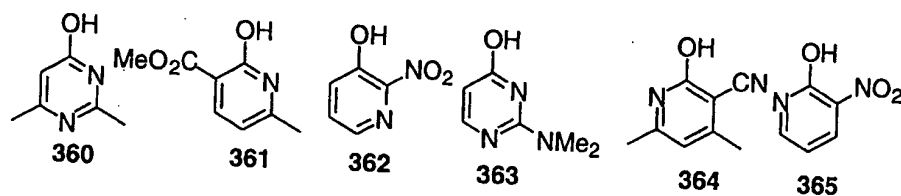
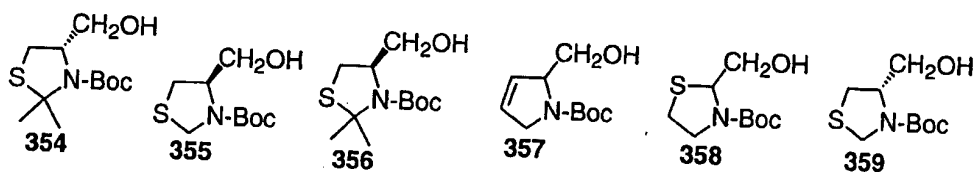


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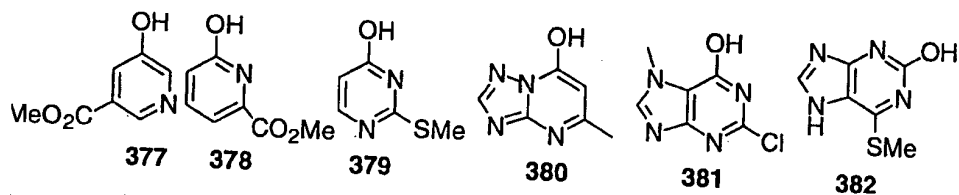
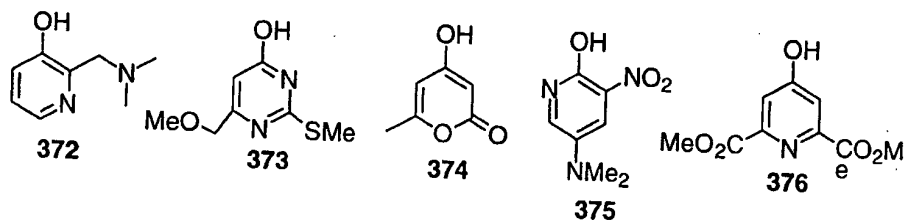
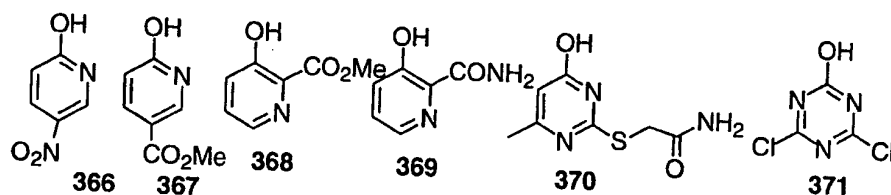




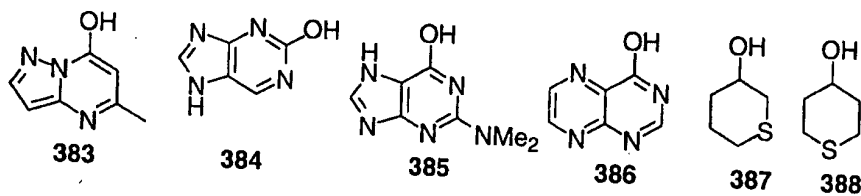
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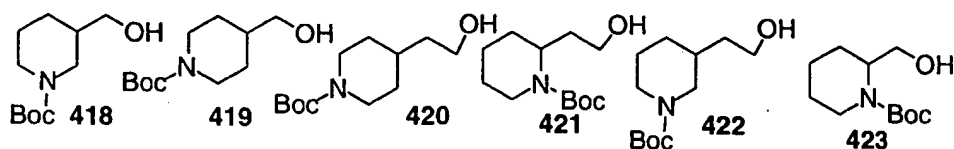
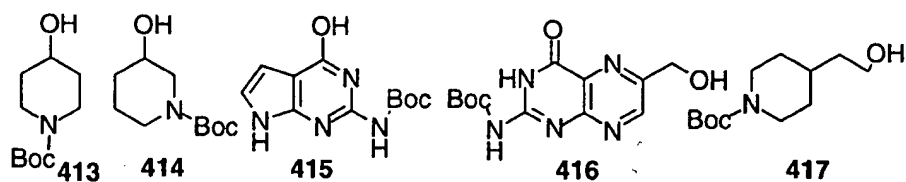
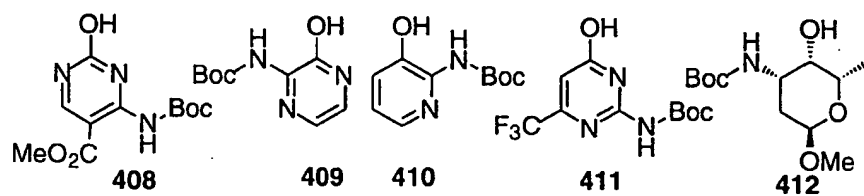
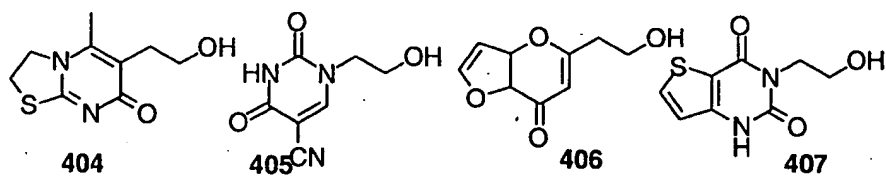
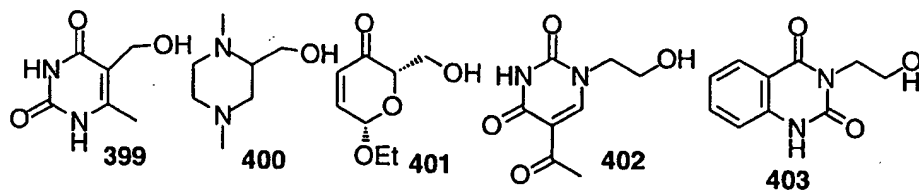
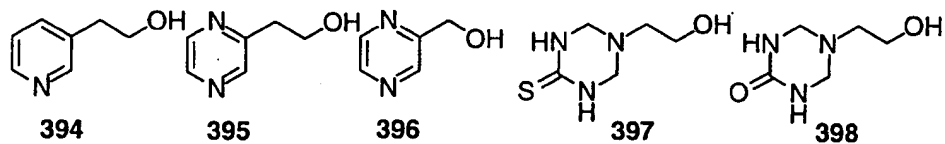
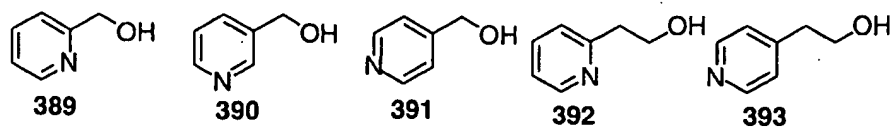


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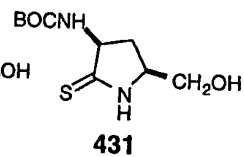
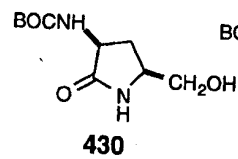
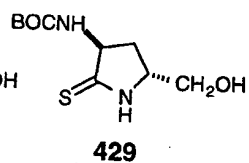
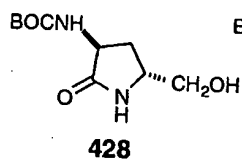
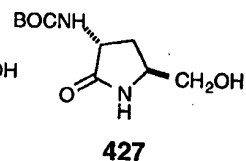
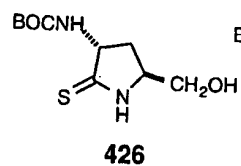
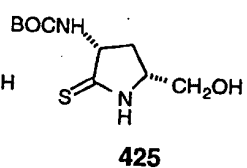
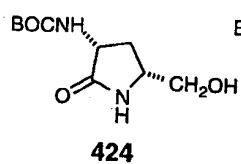




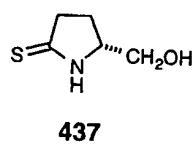
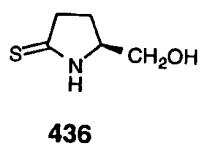
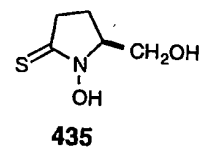
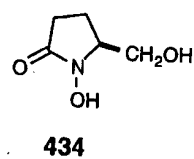
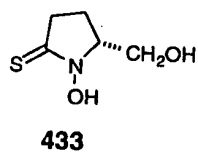
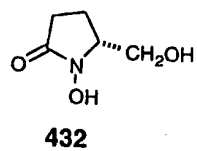
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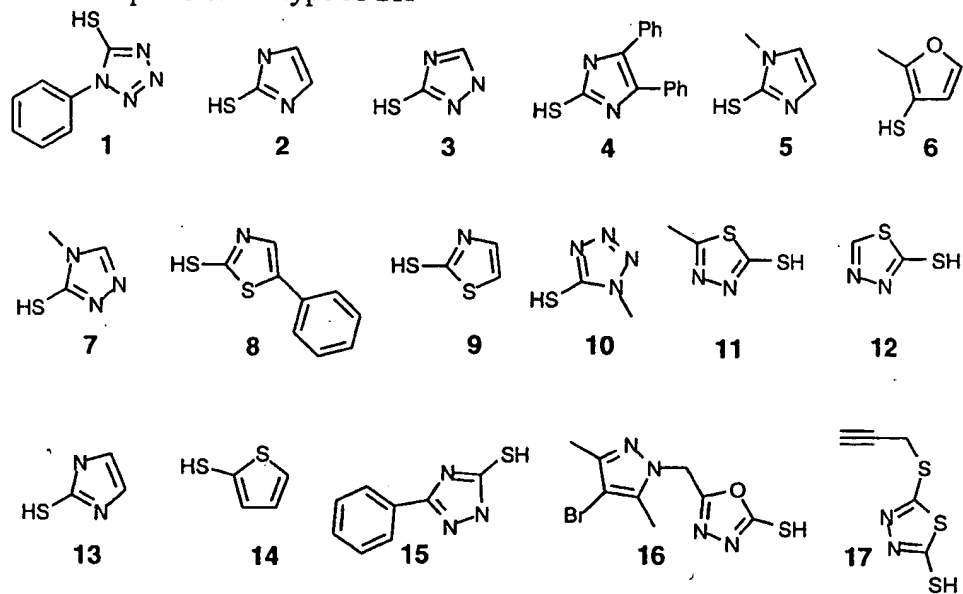
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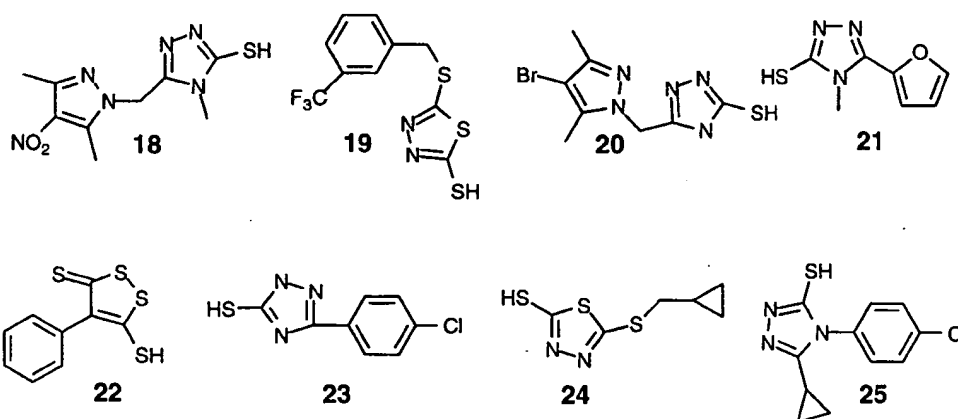
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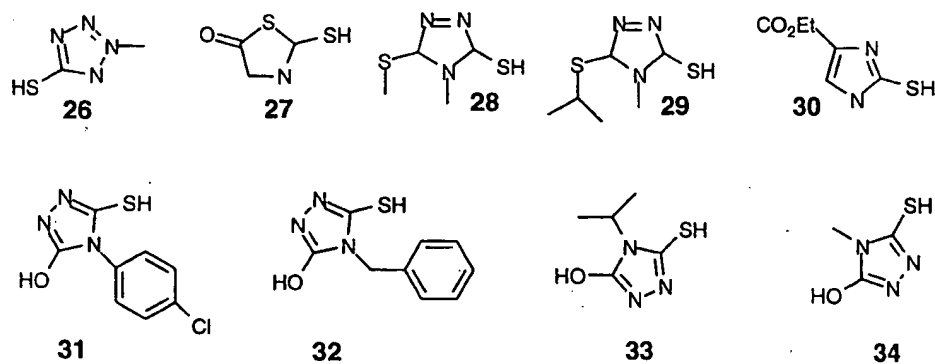
3205 Table 16. Mercaptans of the type A-SH



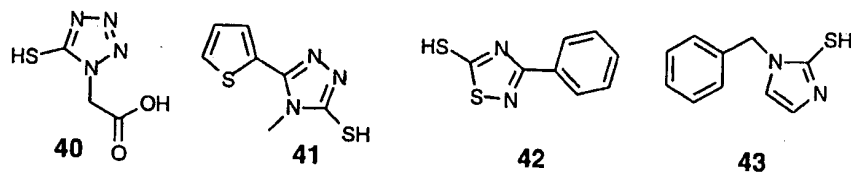
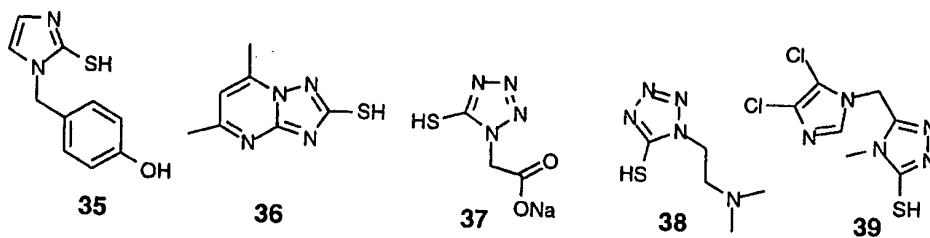
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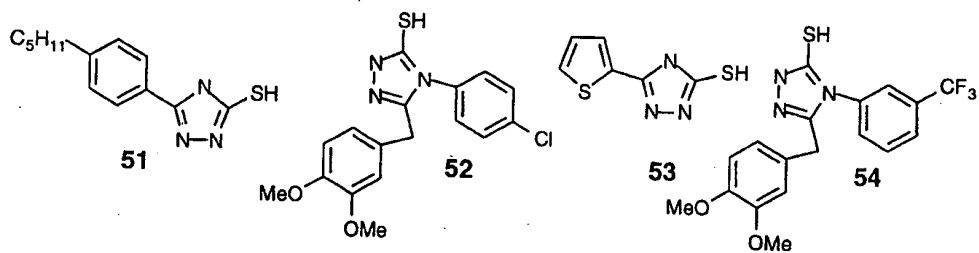
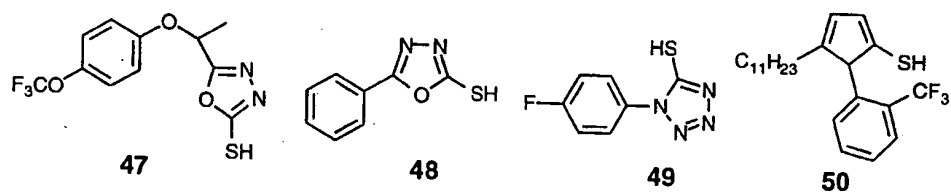
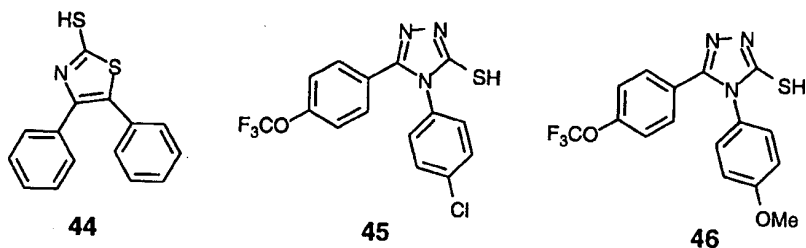
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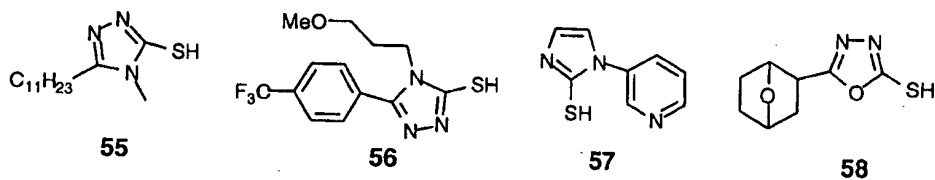
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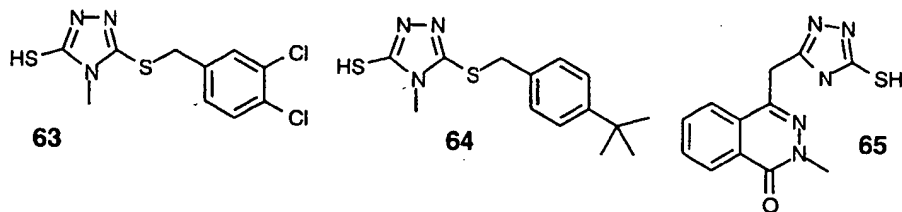
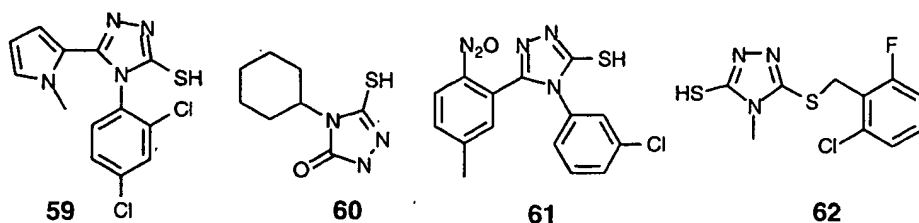


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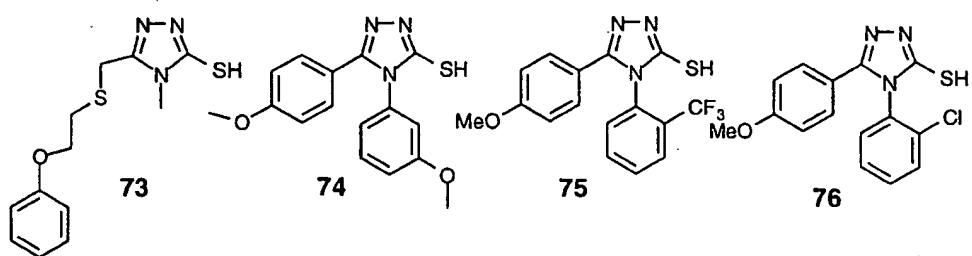
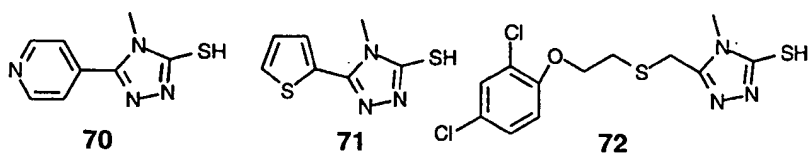
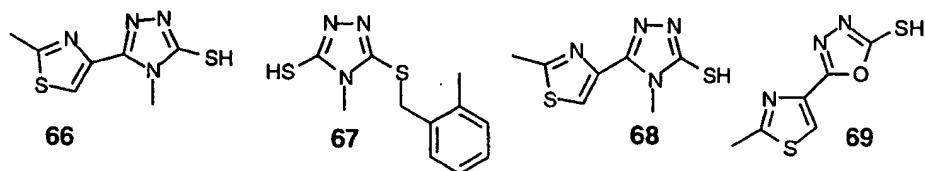


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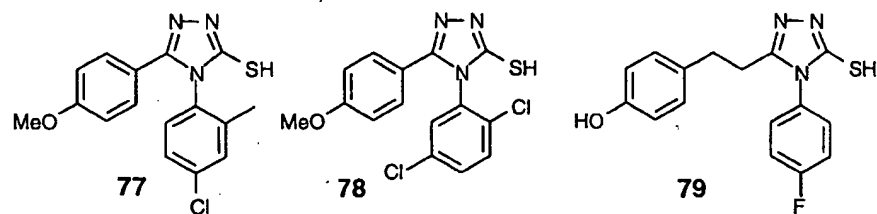




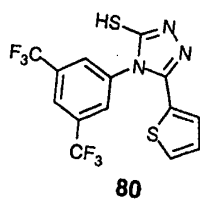
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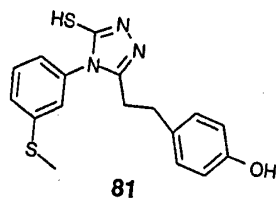
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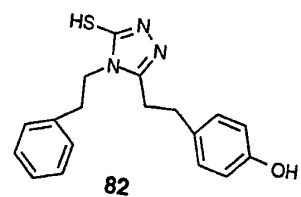
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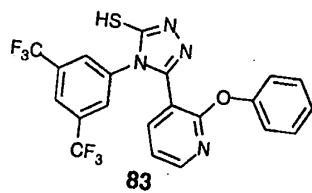
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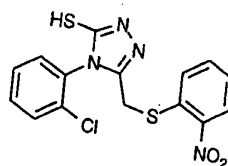
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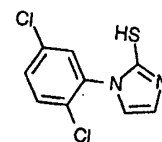
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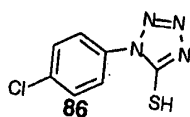
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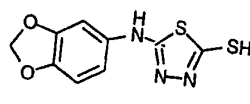
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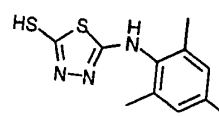
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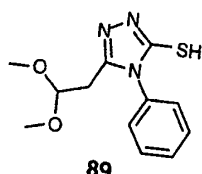
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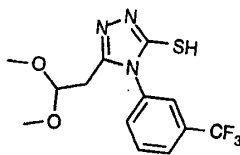
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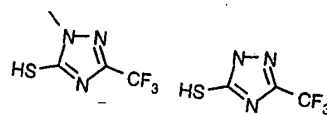
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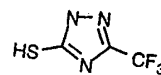
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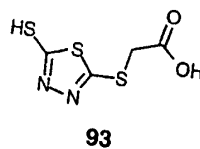
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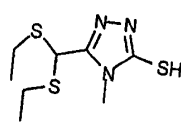
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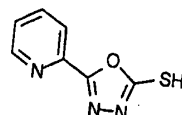
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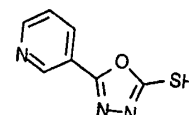
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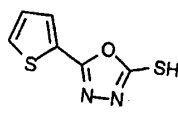
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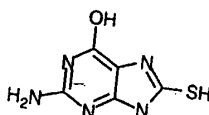
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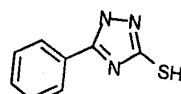
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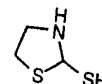
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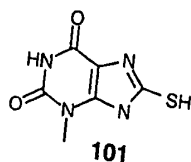
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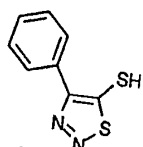
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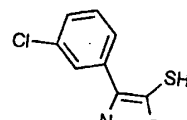
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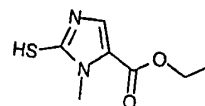
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102

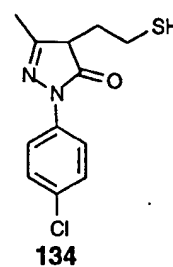
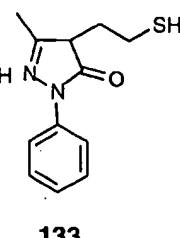
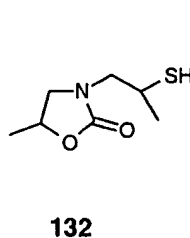
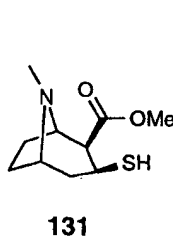
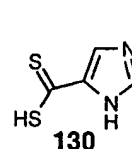
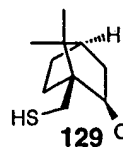
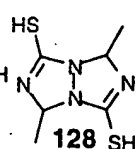
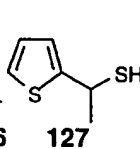
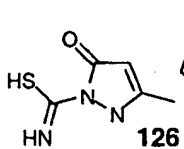
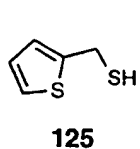
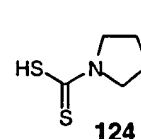
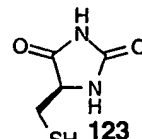
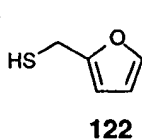
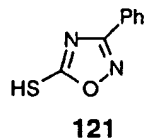
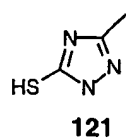
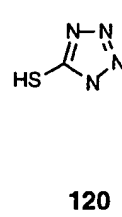
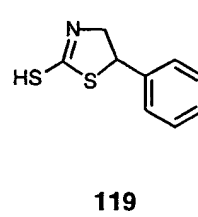
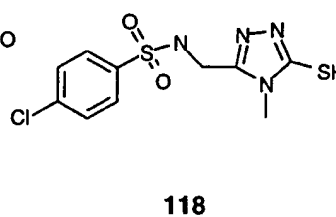
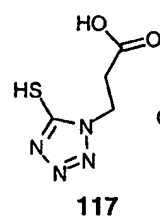
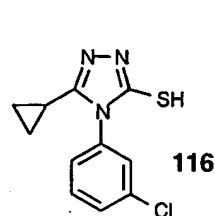
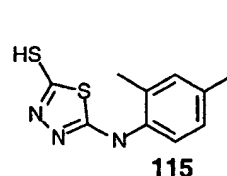
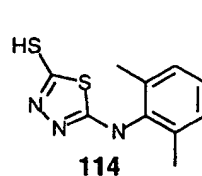
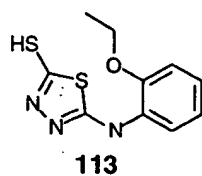
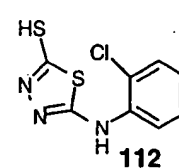
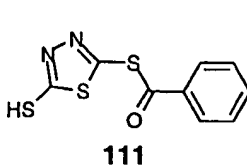
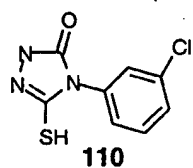
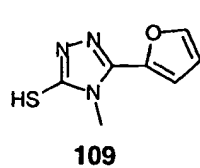
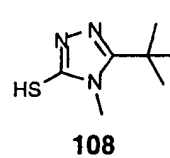
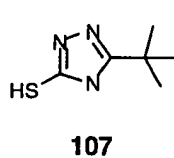
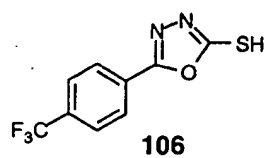
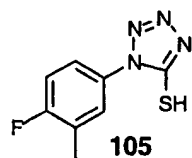


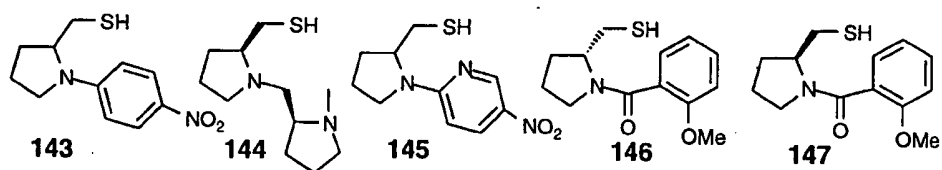
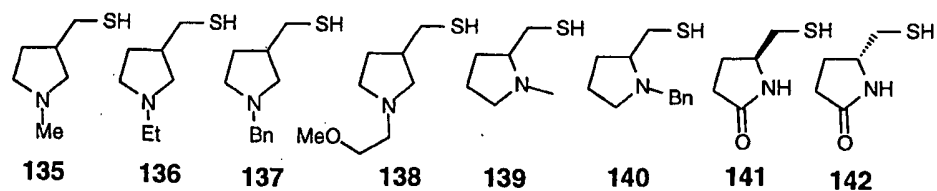
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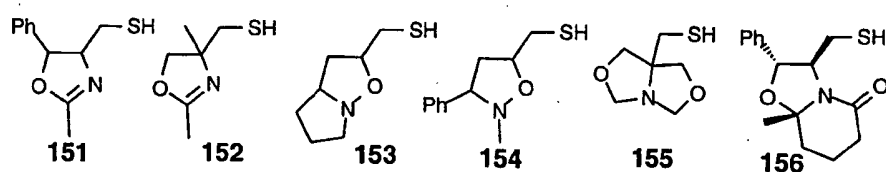
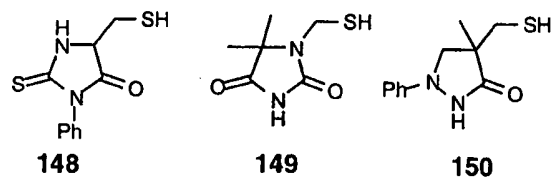
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3255

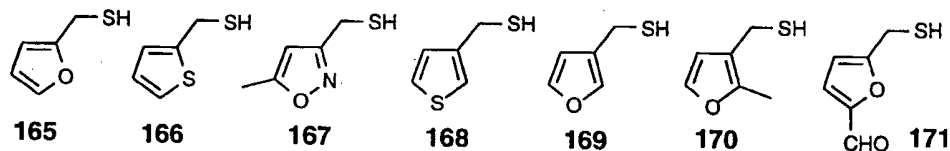
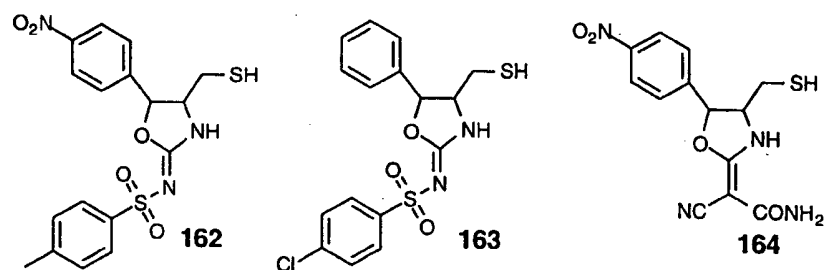
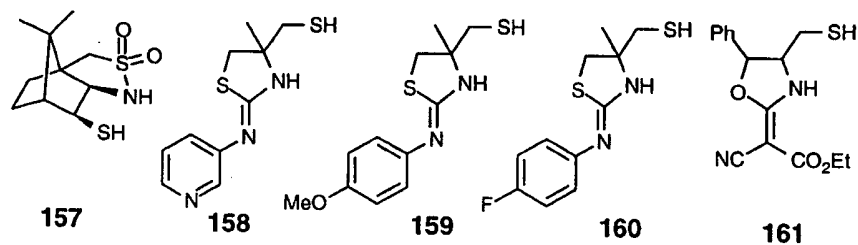




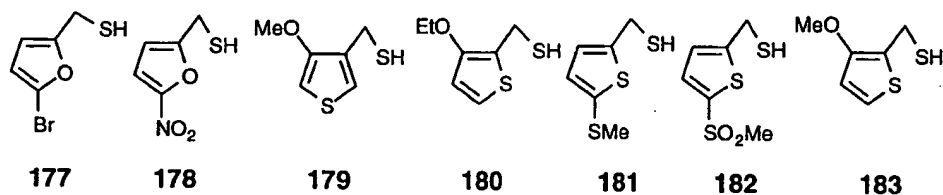
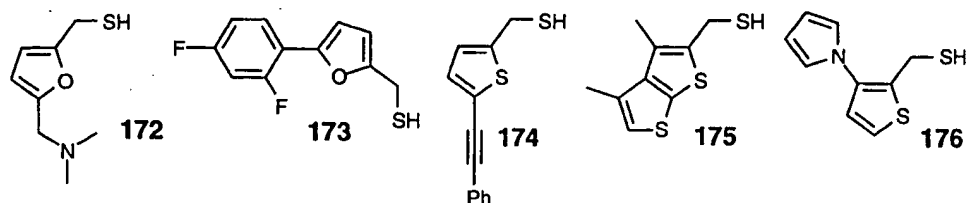
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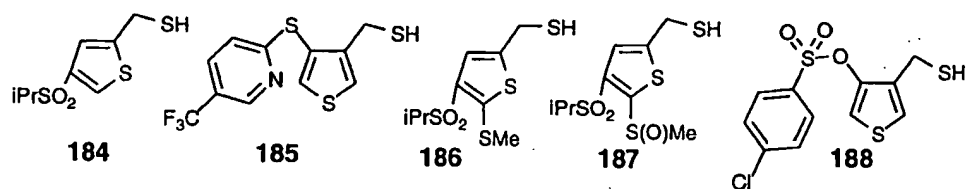
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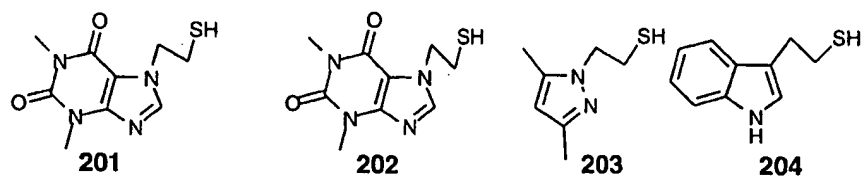
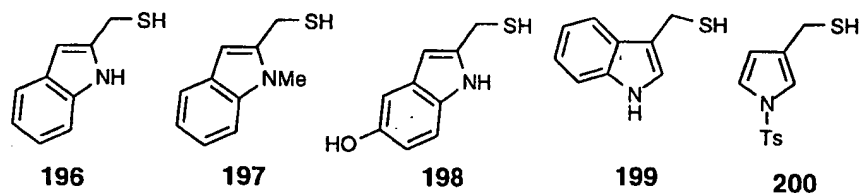
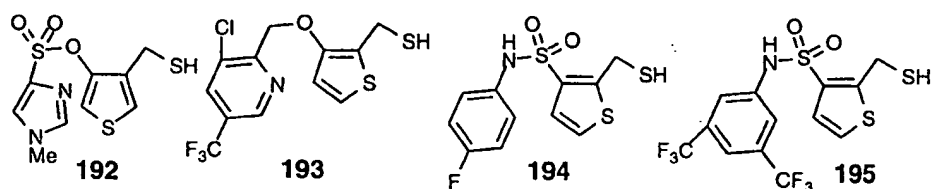
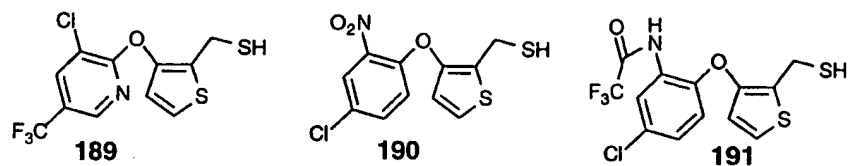
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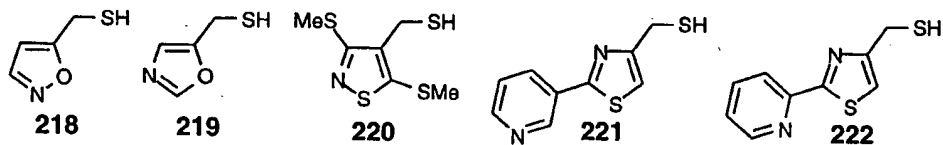
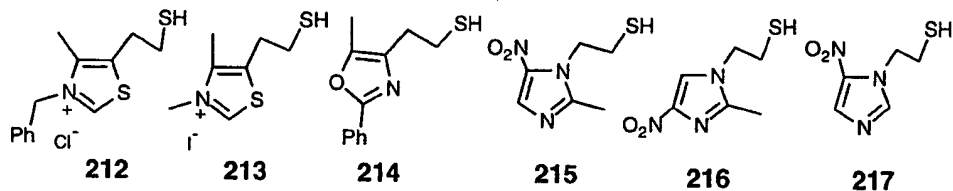
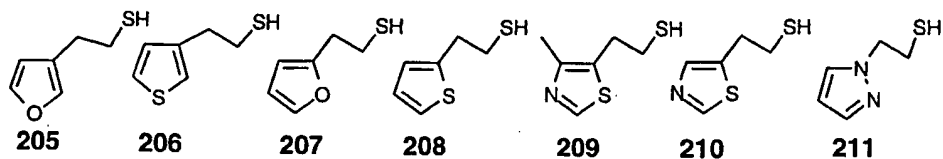
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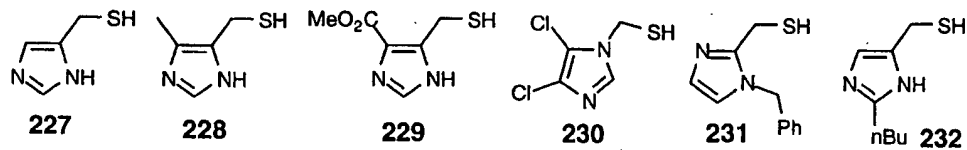
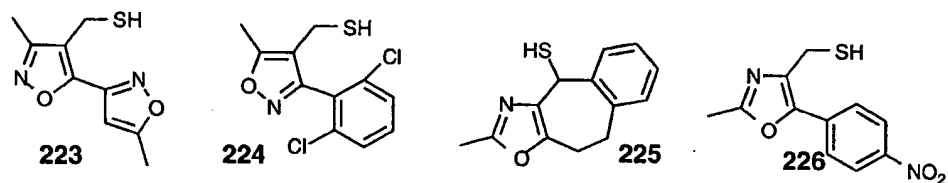
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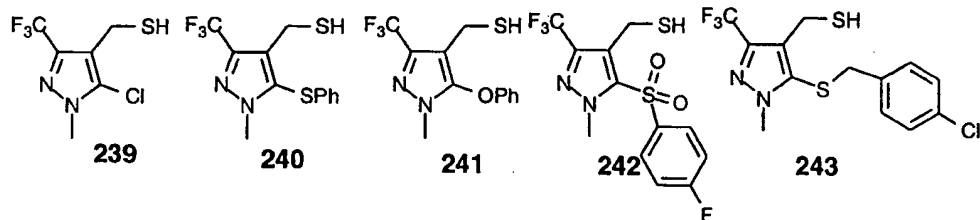
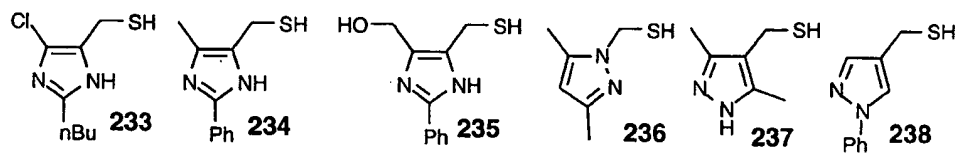
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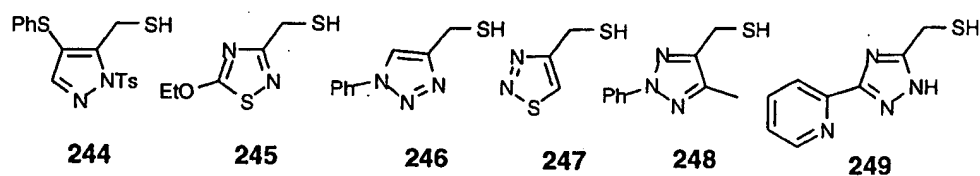


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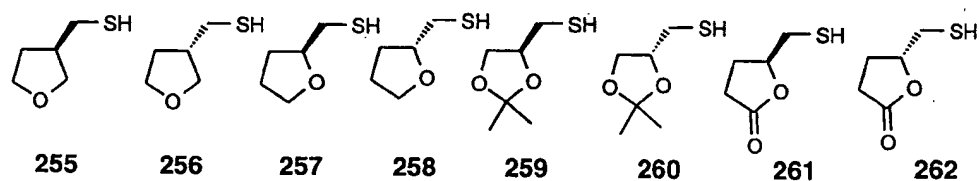
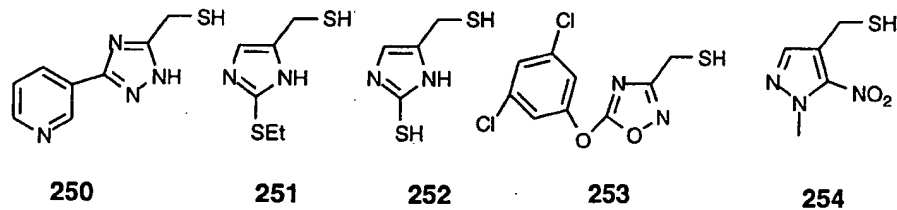


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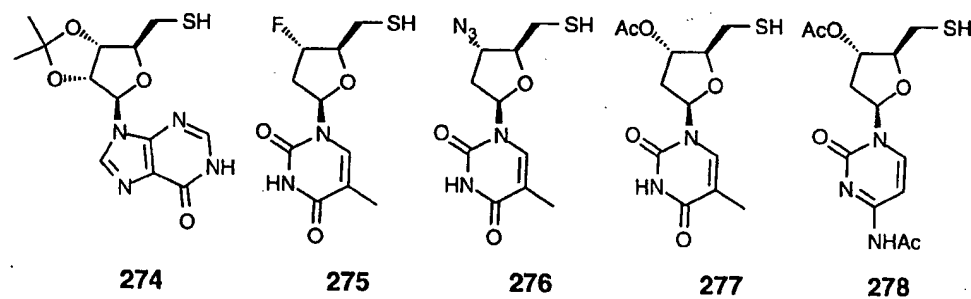
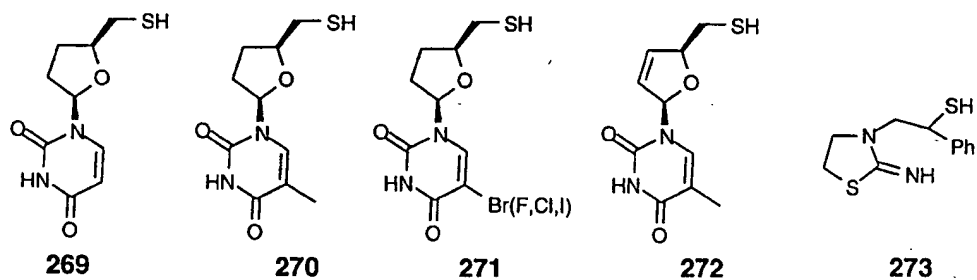
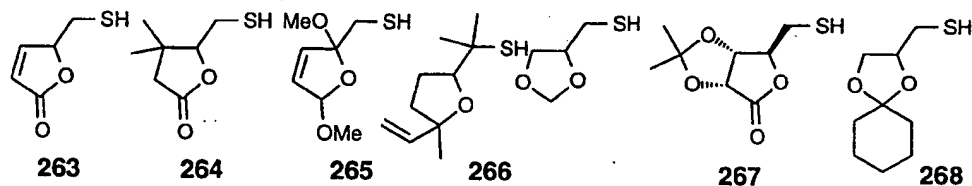




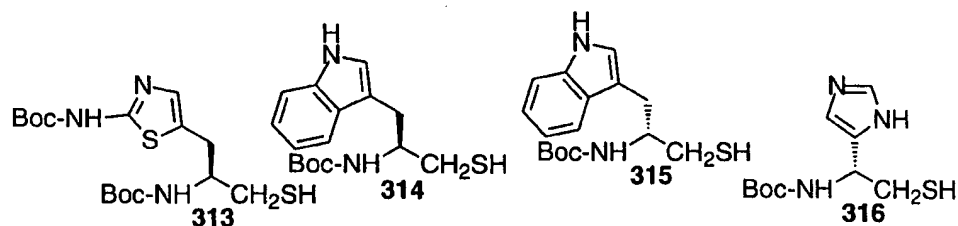
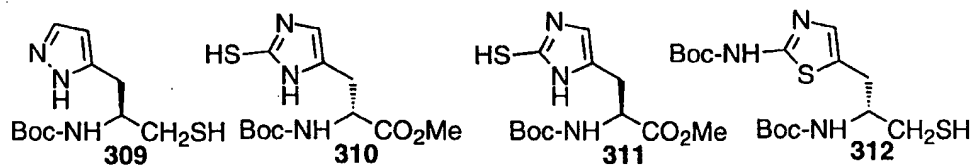
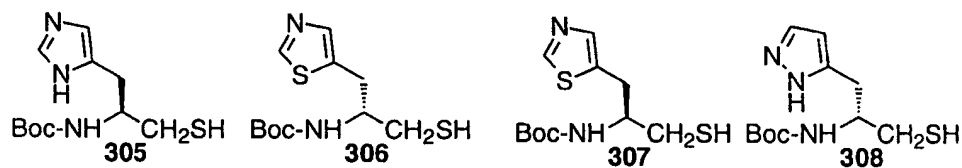
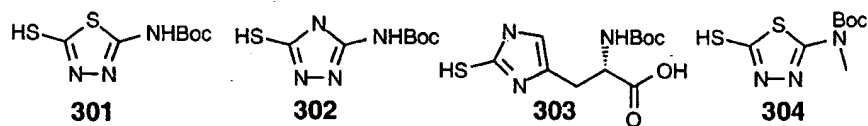
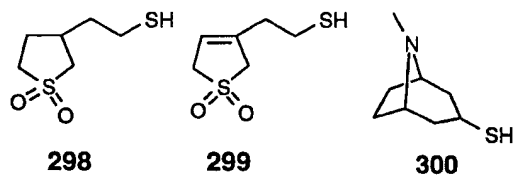
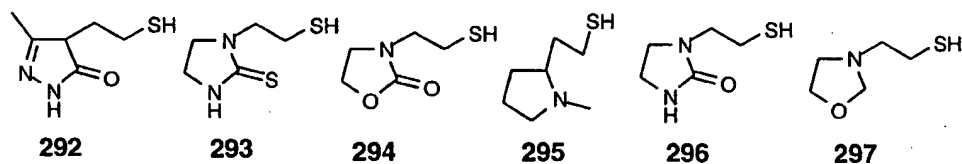
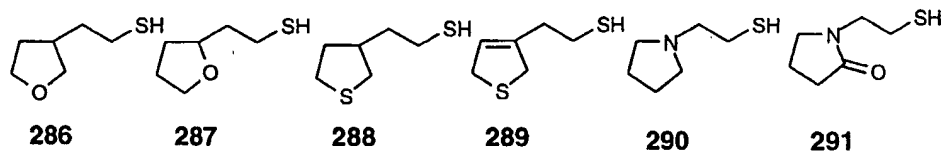
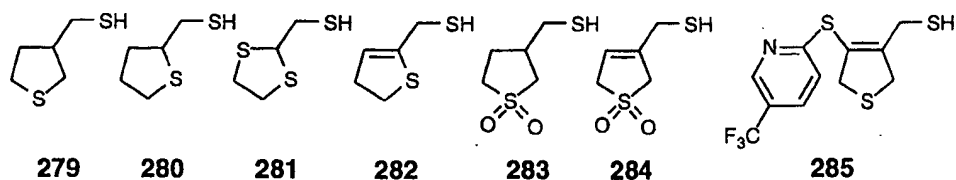
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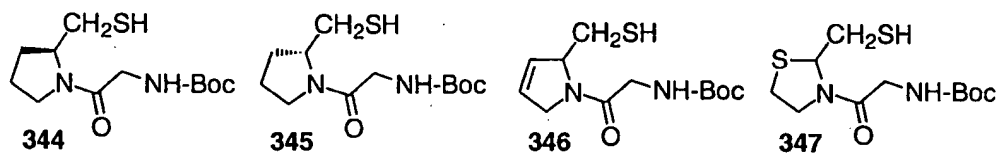
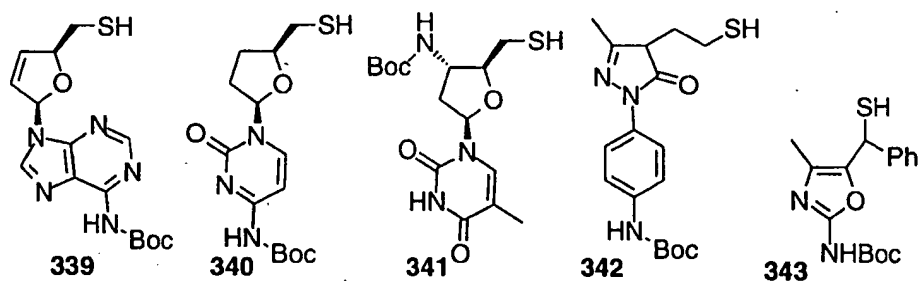
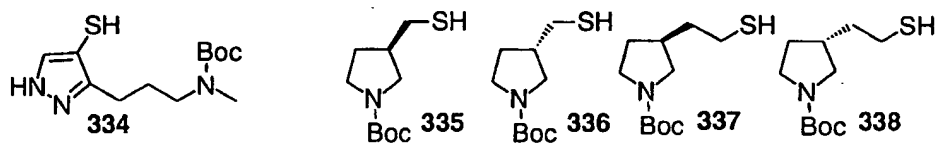
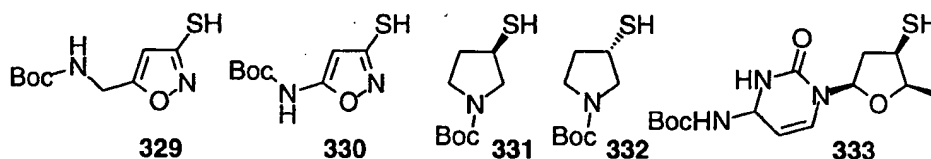
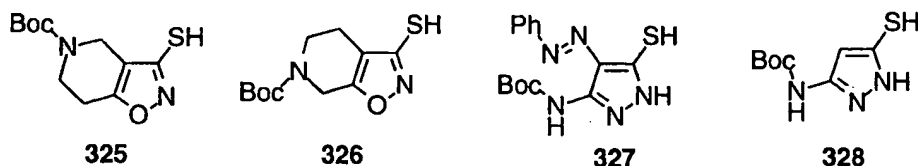
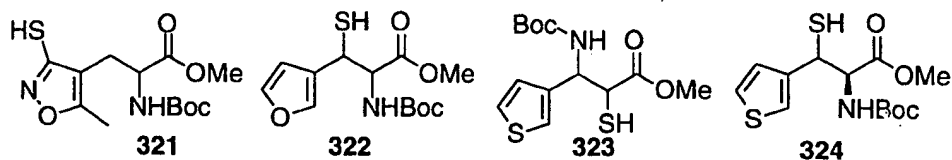
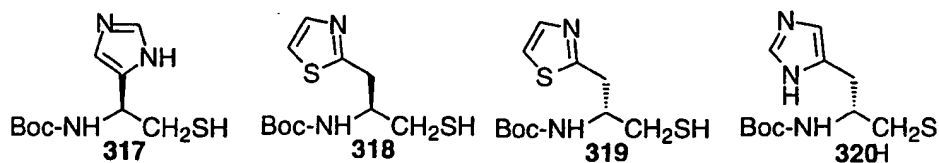


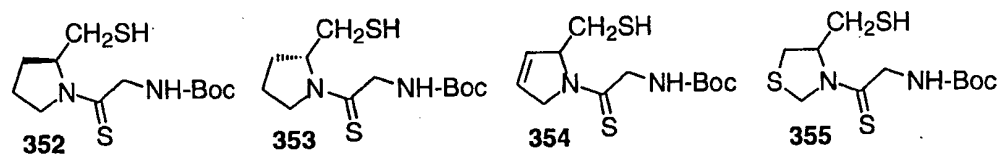
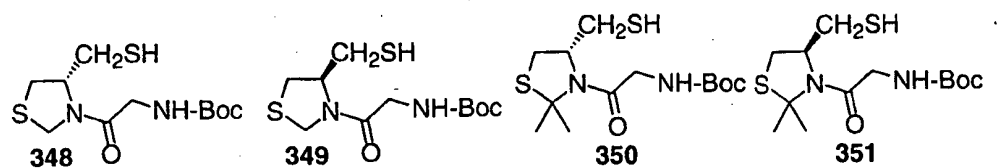
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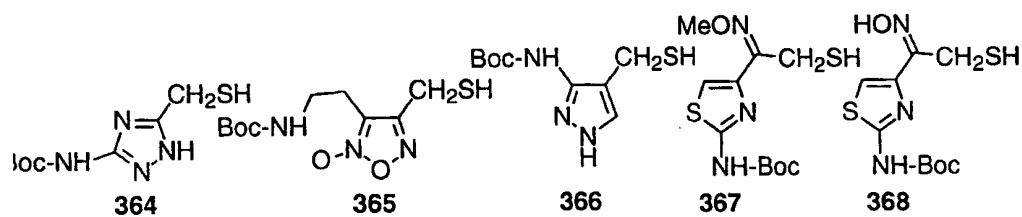
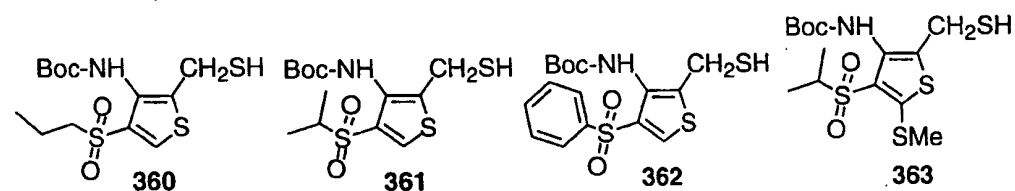
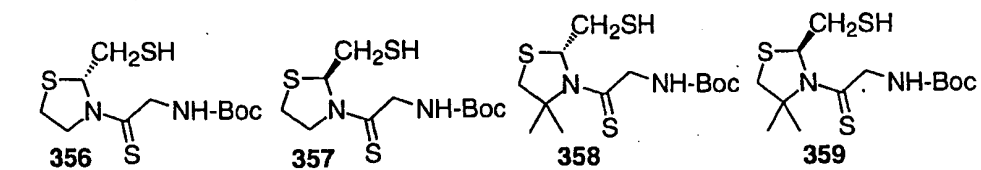
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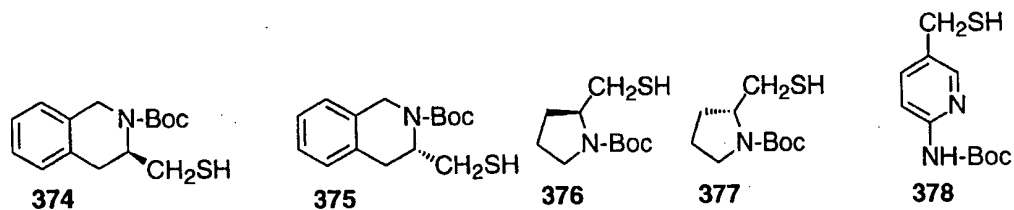
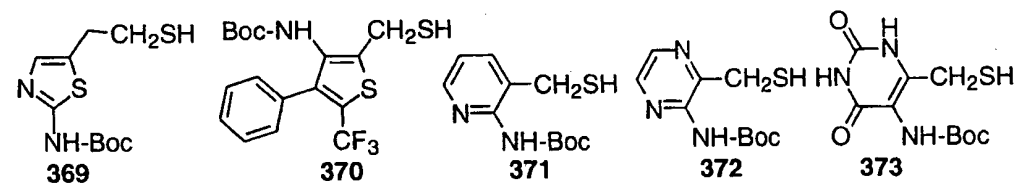




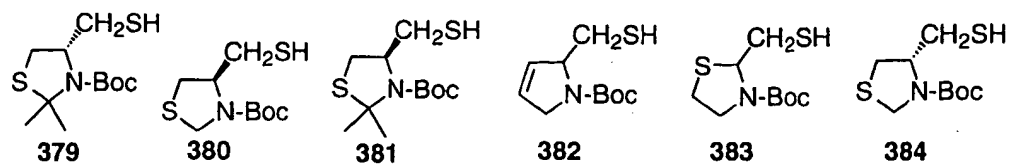
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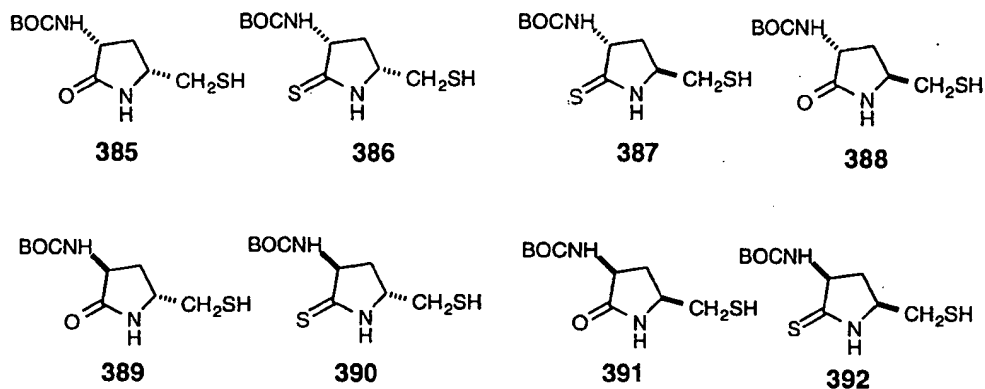
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3370



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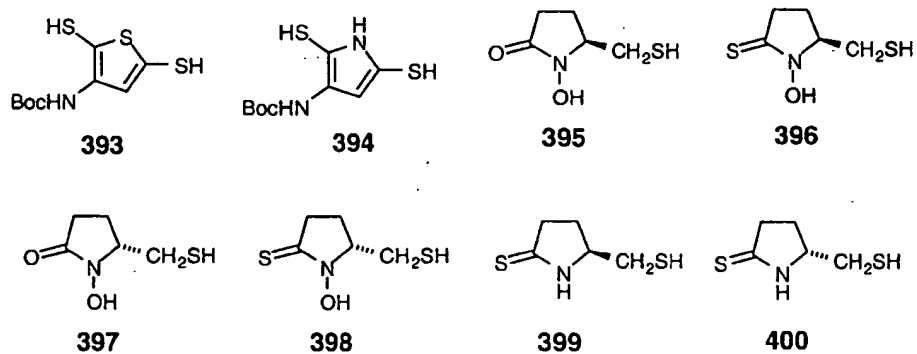
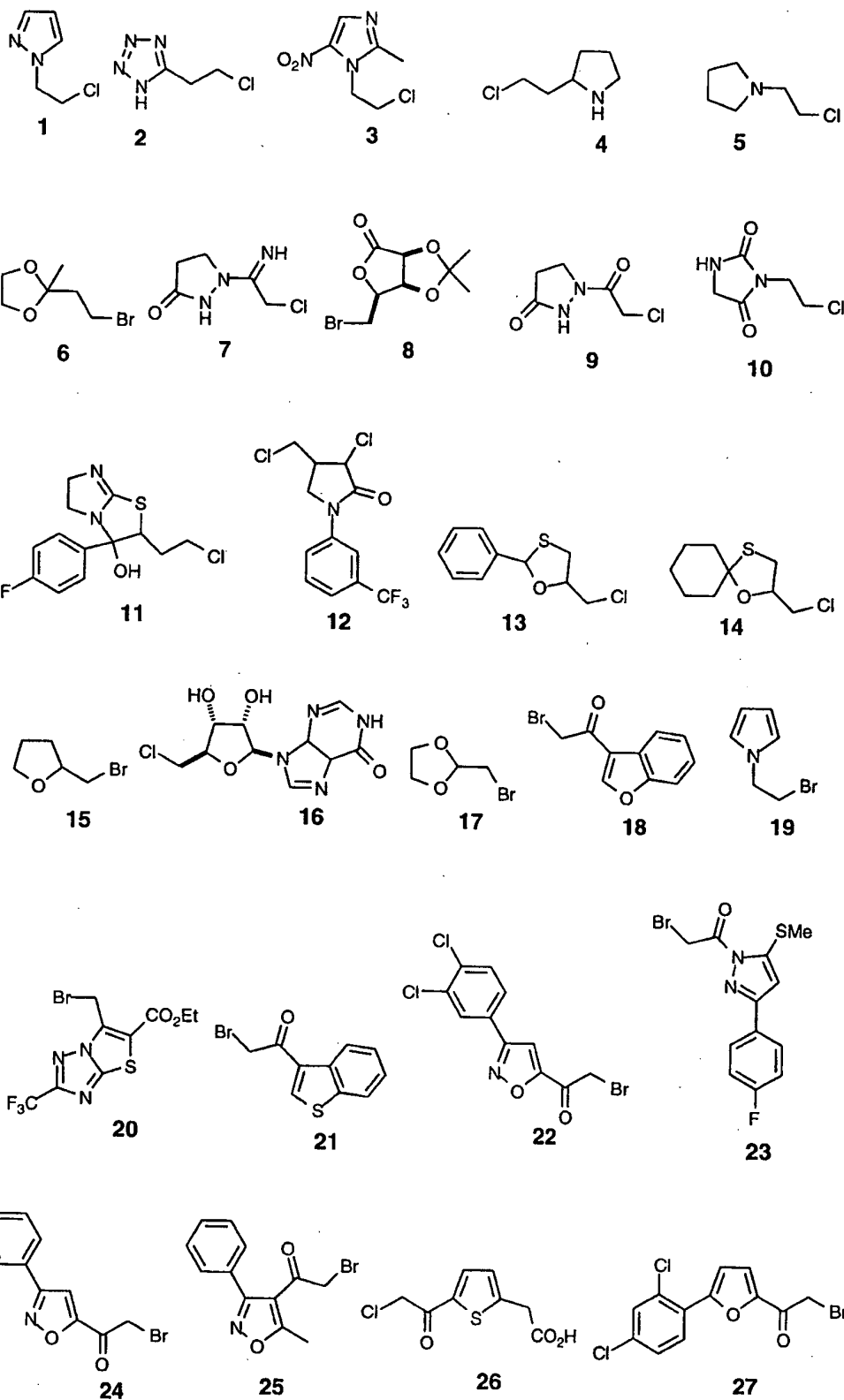
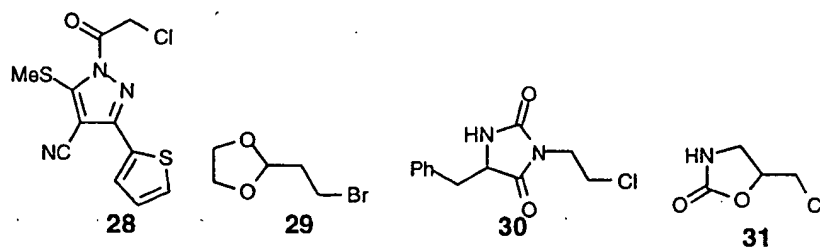
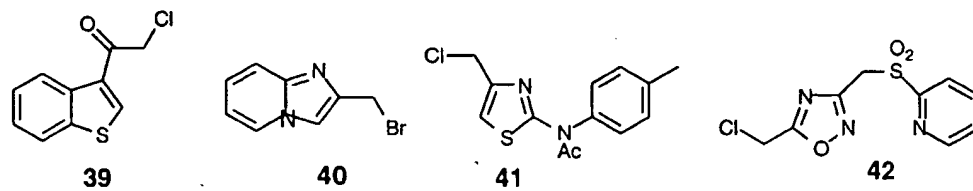
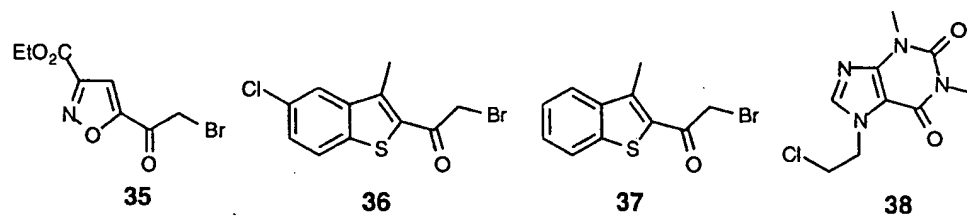
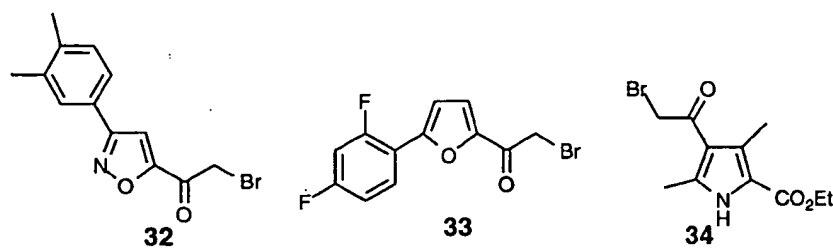


Table 17. Halides of the type A-Cl, A-Br, and A-I

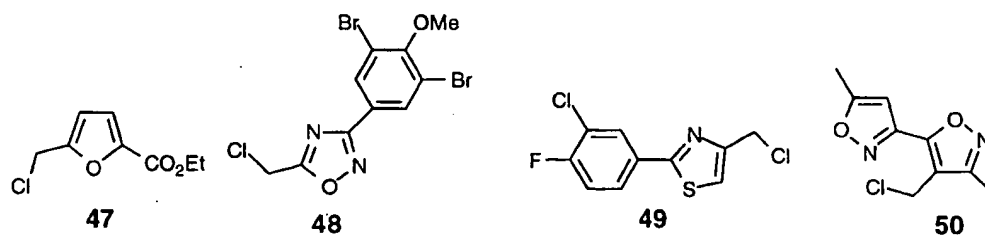
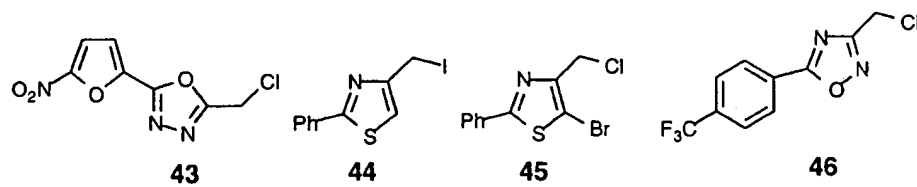




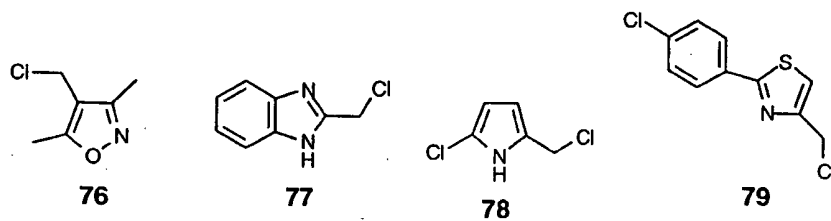
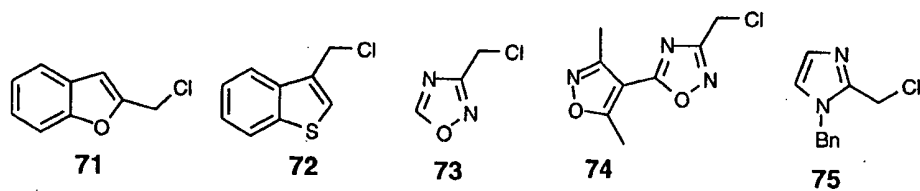
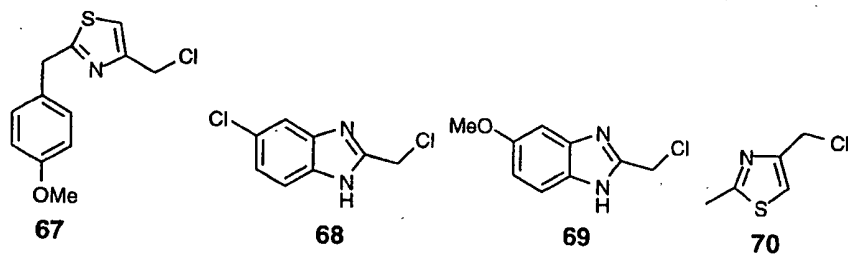
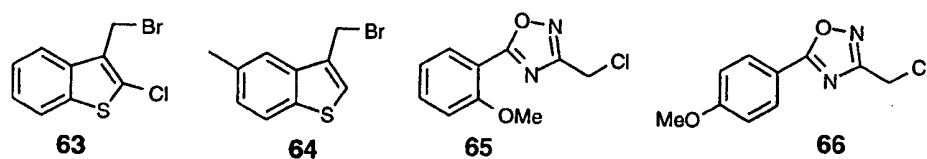
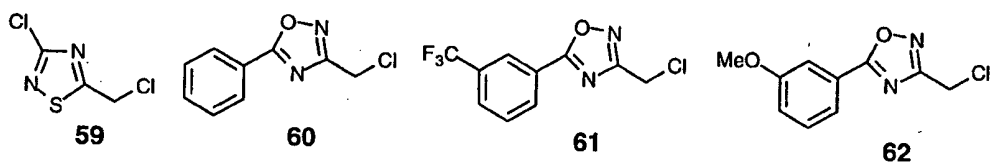
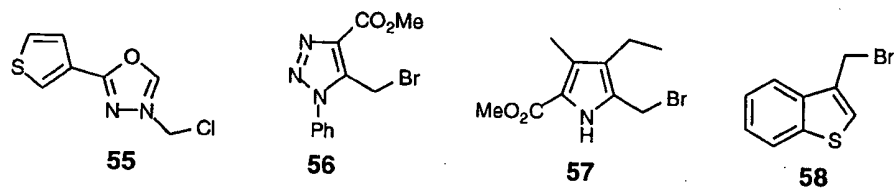
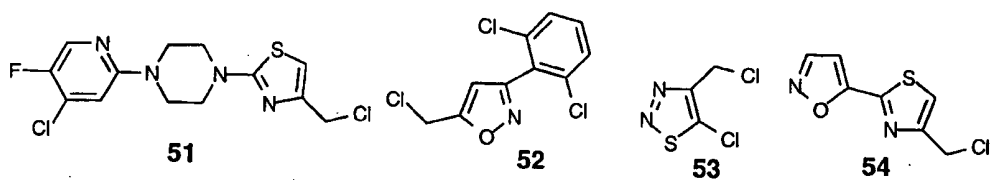
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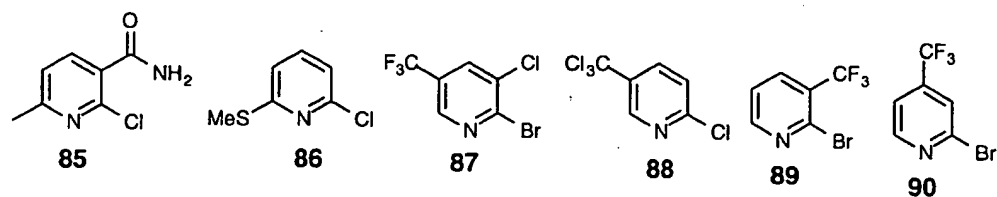
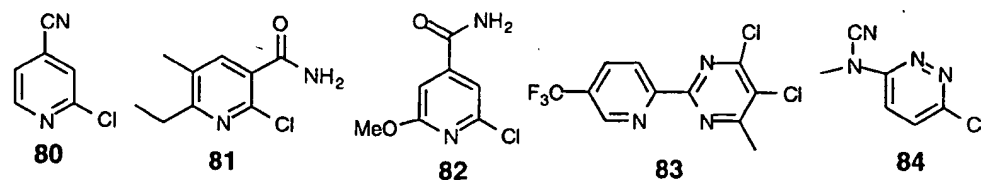
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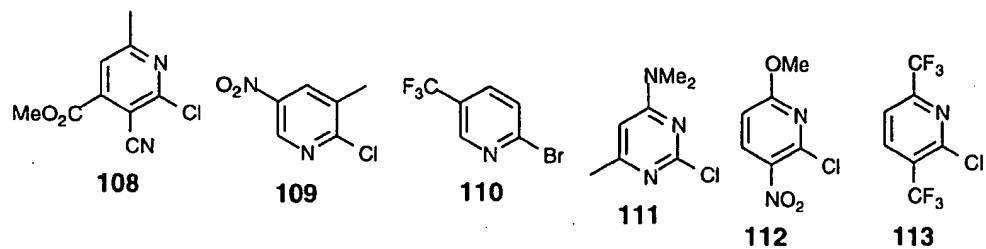
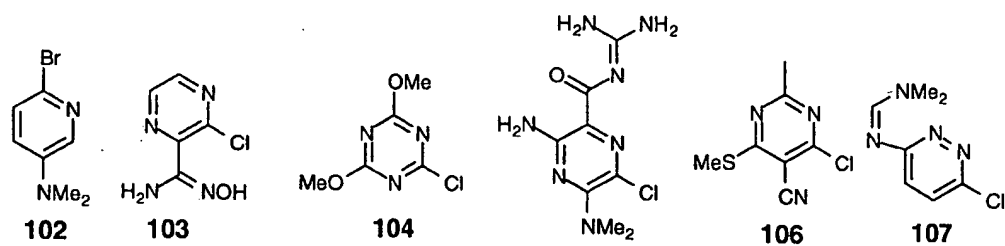
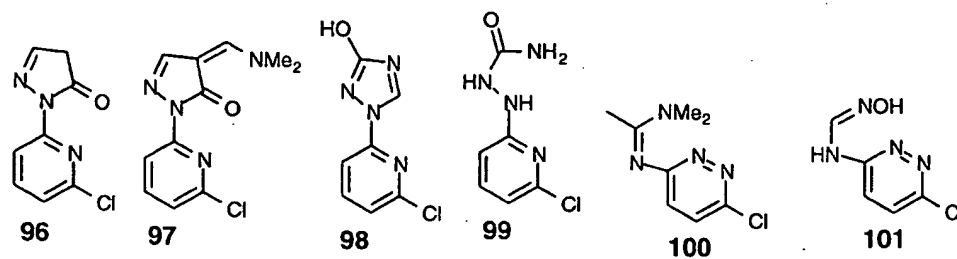
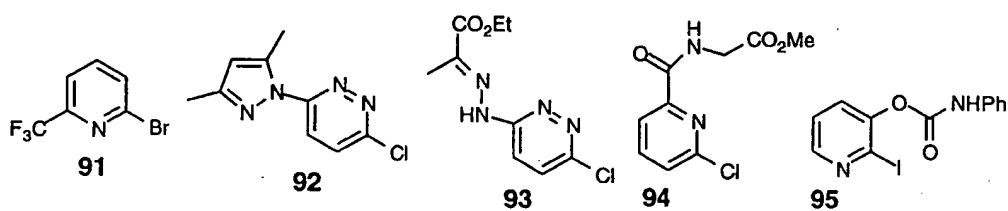
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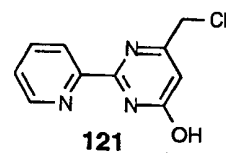
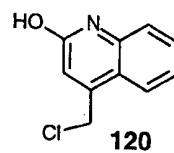
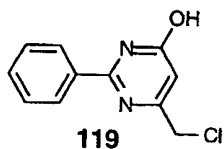
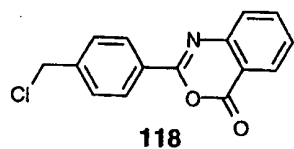
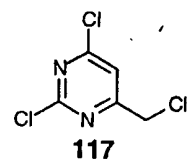
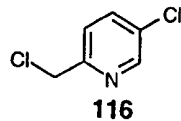
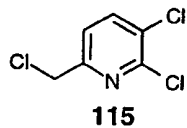
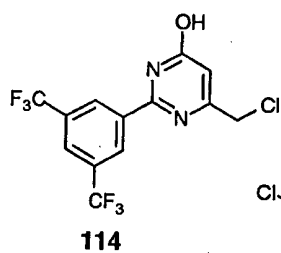
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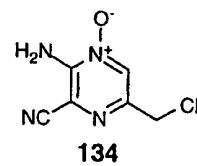
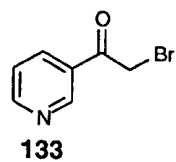
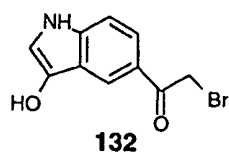
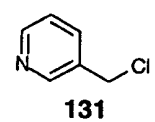
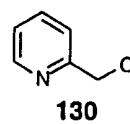
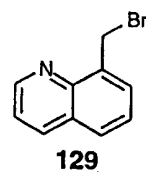
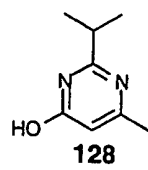
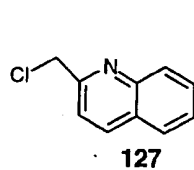
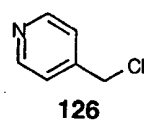
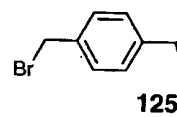
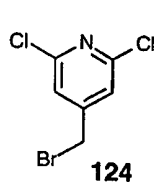
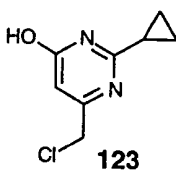
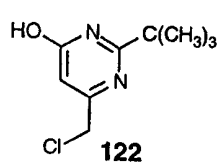
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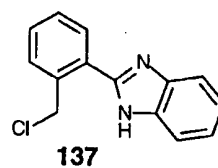
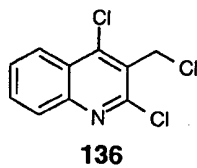
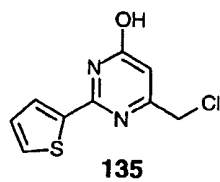
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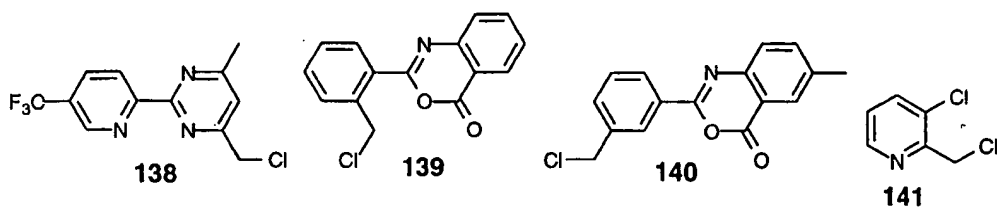


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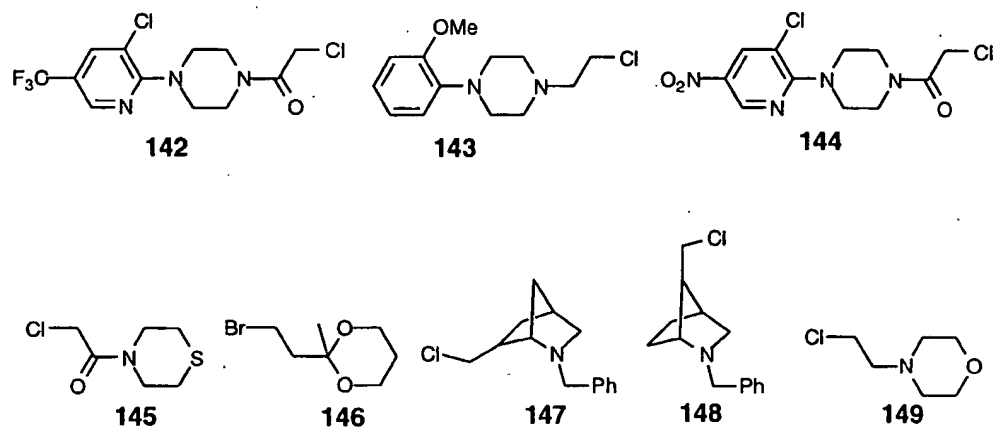


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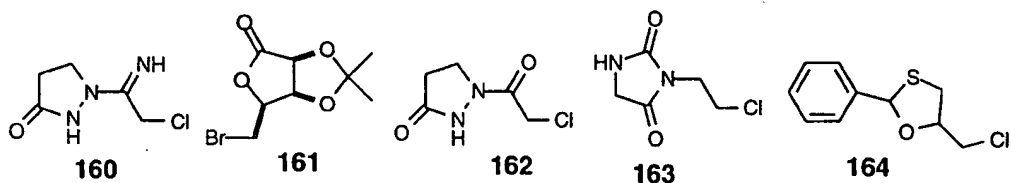
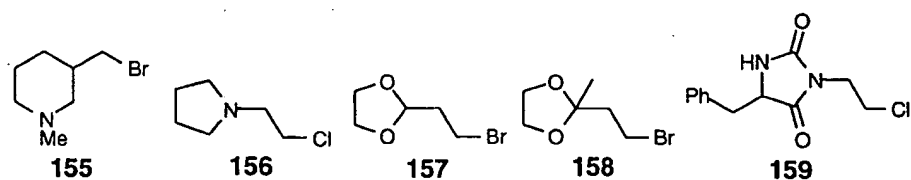
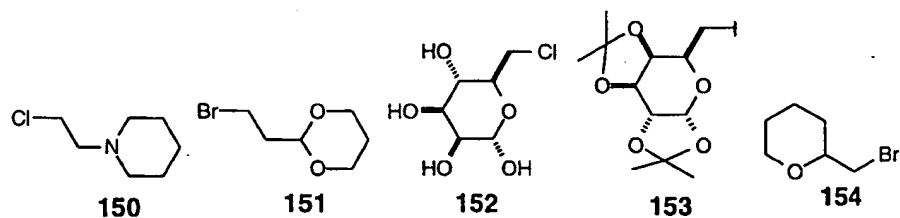




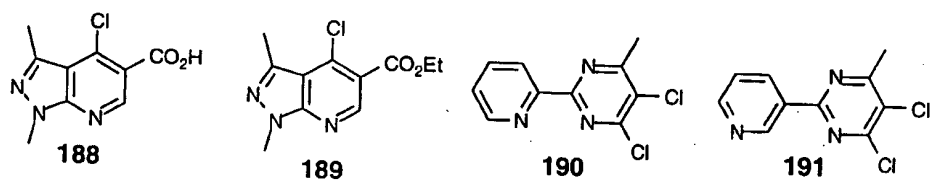
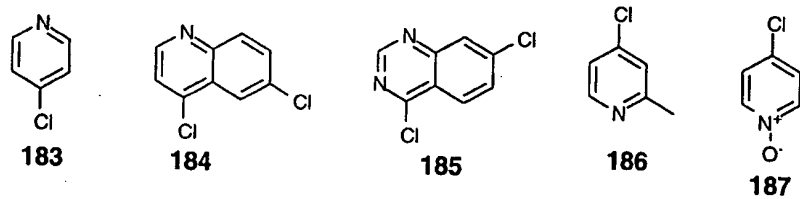
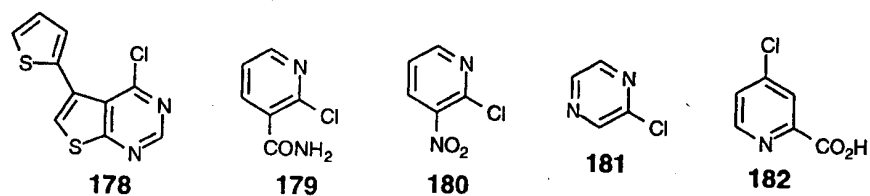
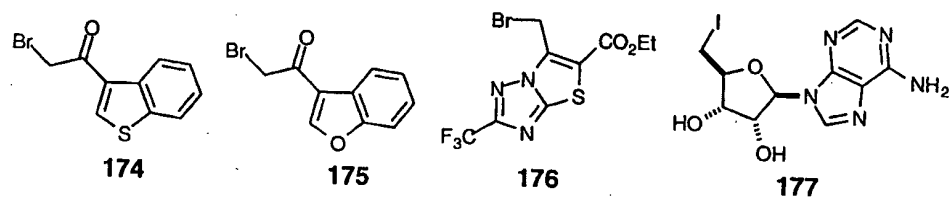
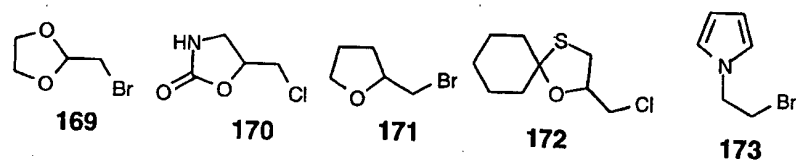
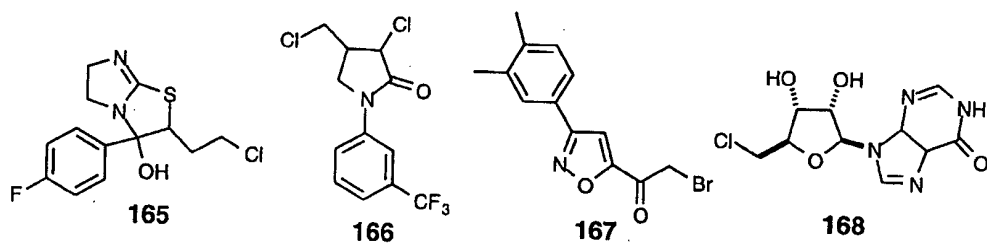
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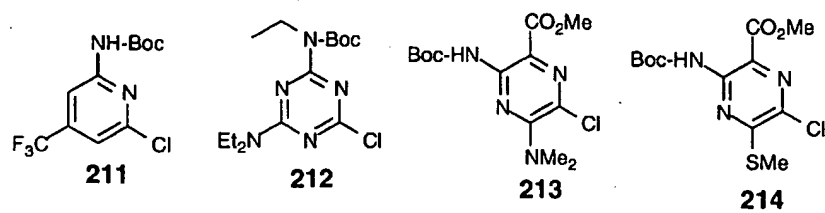
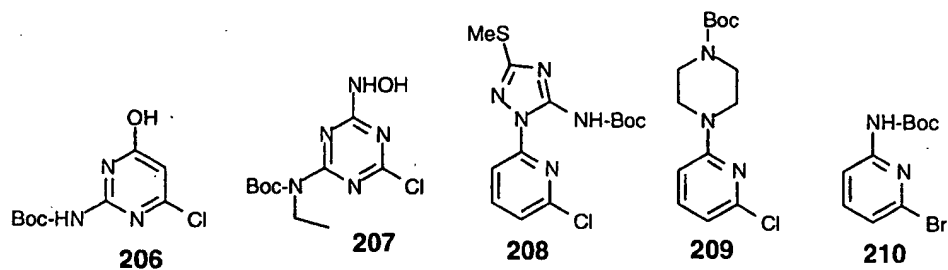
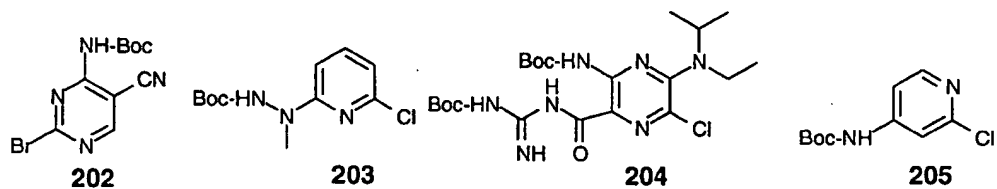
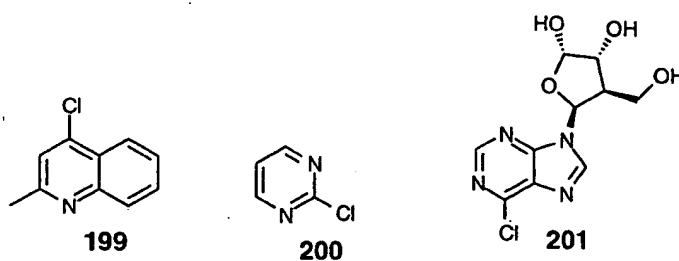
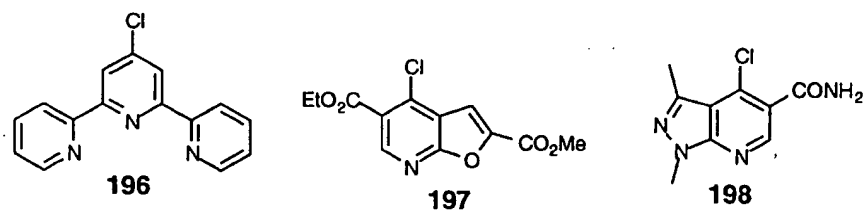
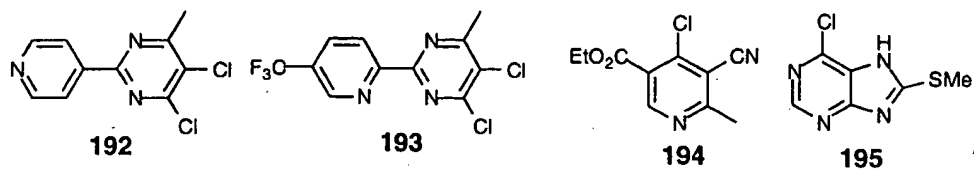


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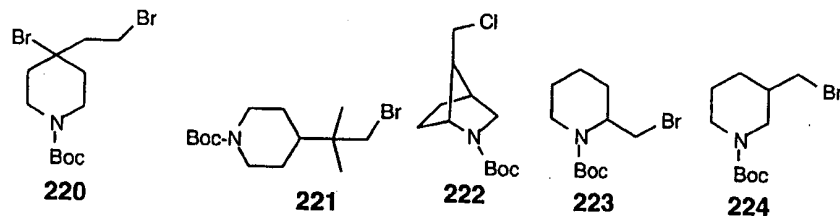
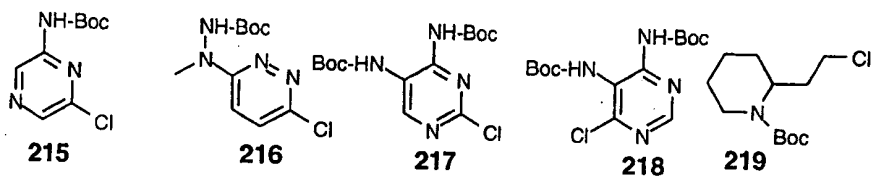


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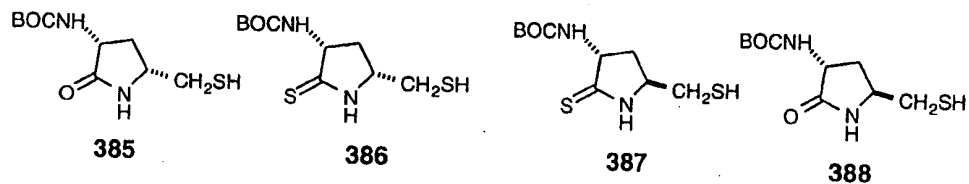
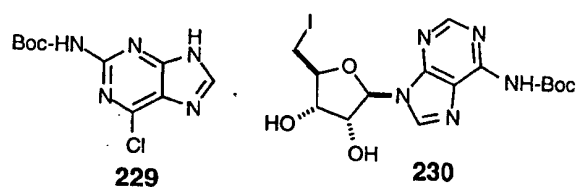
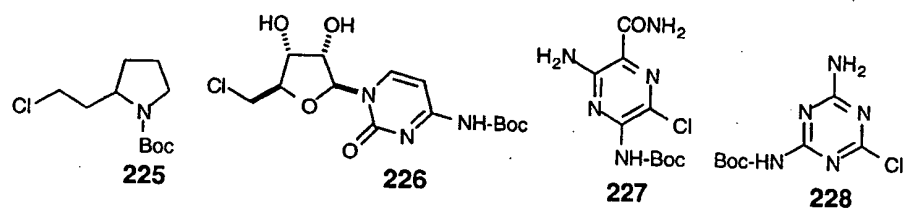




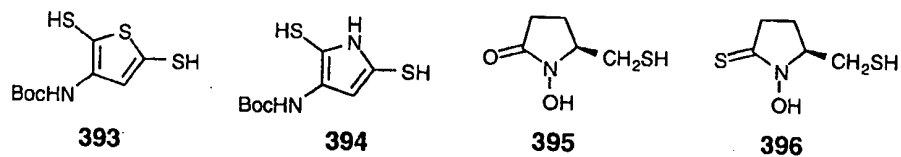
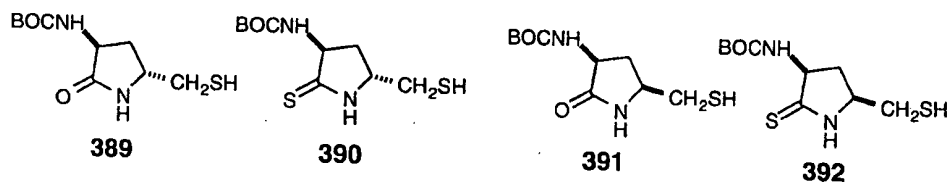
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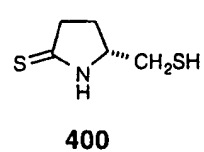
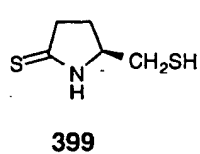
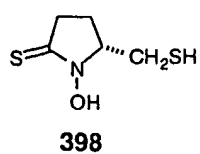
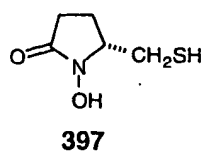


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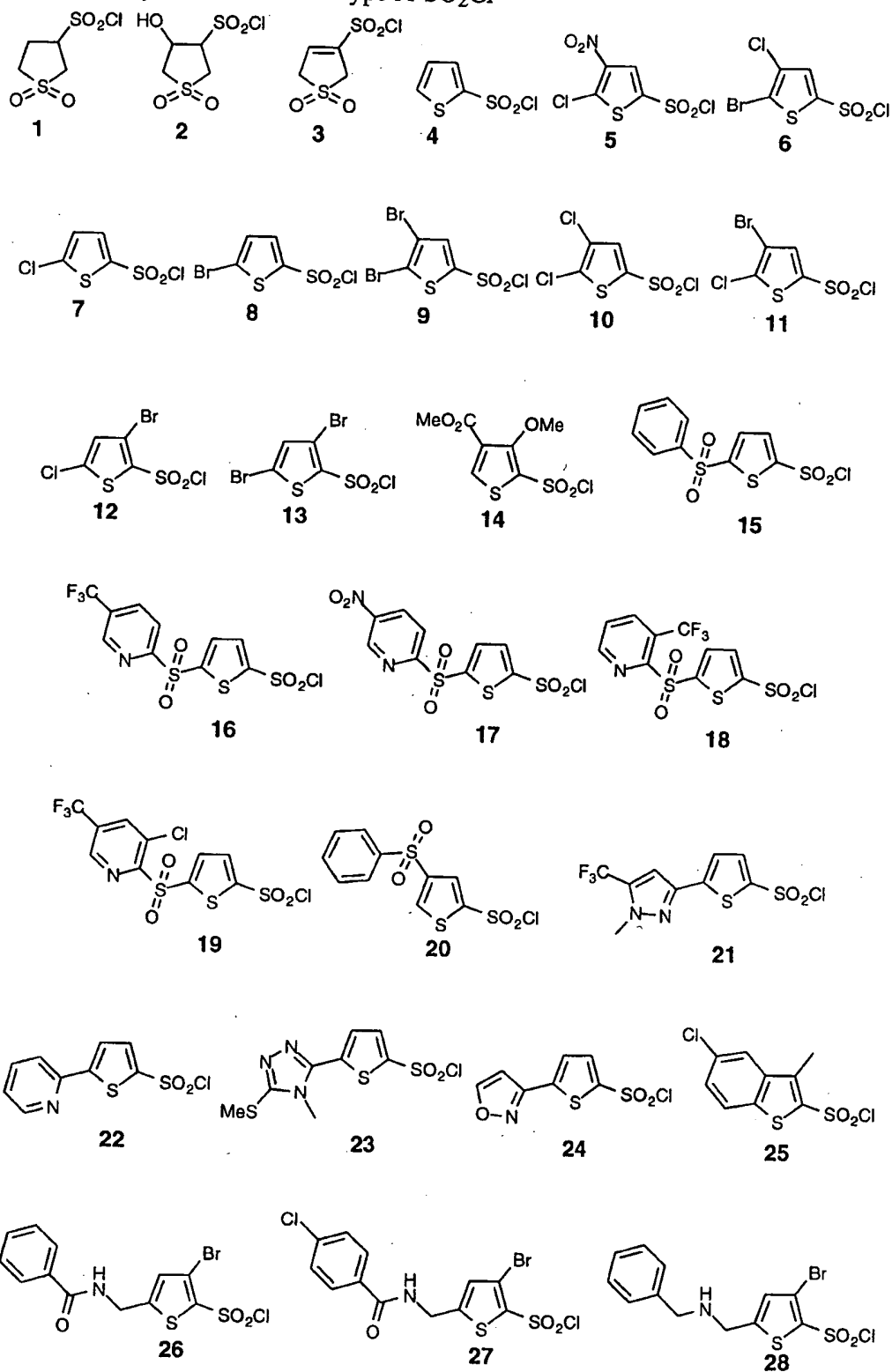


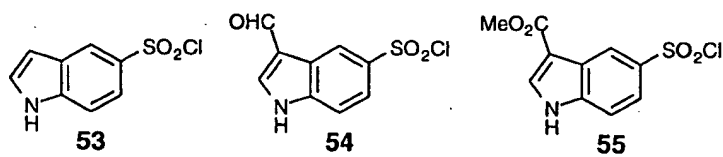
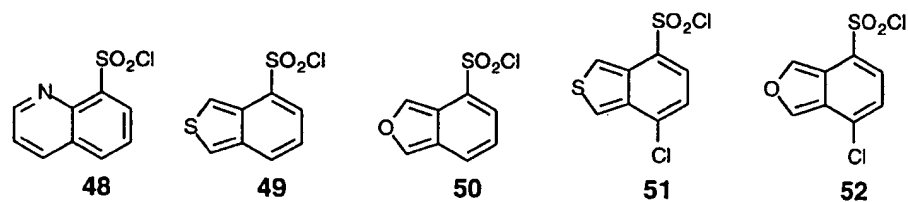
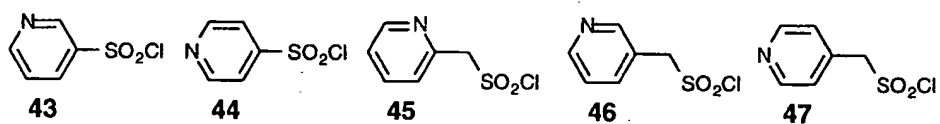
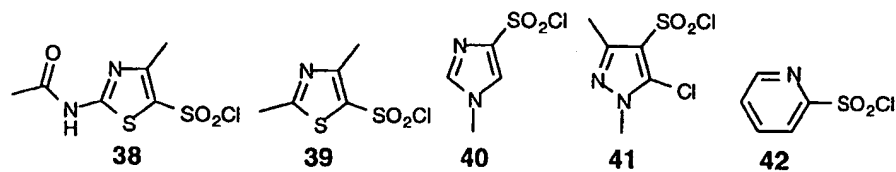
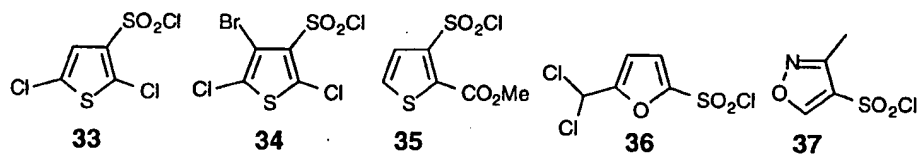
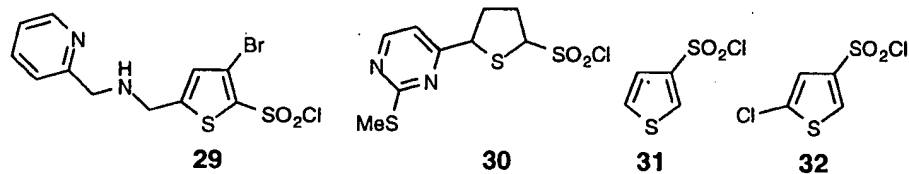
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Table 18. Sulfonyl chlorides of the type A-SO₂Cl



The foregoing may be better understood by reference to the following examples which are provided for illustration and not intended to limit the scope of the inventive concept.

3525 In Tables 2-10, the abbreviation bz=benzoyl, bn=benzyl, Ph=phenyl, BOC=t-butyloxycarbonyl and TS=p-toluenesulfonyl.

Compound 1

(3-(Aminomethyl)benzoyl)-Met-OCH₃

3530

Step A

(3-(Chloromethyl)benzoyl)-Met-OCH₃

To a solution of methionine methyl ester hydrochloride (2.0 g, 10 mmol) and 3-(chloromethyl)benzoyl chloride (2.08 g, 11.0 mmol) in methylene chloride (50 mL) was slowly added triethylamine (3.07 mL, 22.0 mmol) at ice bath temperature for 2 hours. The mixture was washed with 0.5 N HCl (50 mL x 2), brine (50 mL x 2) and water (50 mL x 2) then dried over anhydrous MgSO₄ and concentrated under reduced pressure. The residue was purified by flash column chromatography (30% ethyl acetate in hexanes) to give the desired product (3.03 g) as a white solid: m.p. 82-83°C; ¹H NMR (CDCl₃) δ 7.82 (1H, s), 7.74 (1H, d, J=7.7 Hz), 7.53 (1H, d, J=7.7 Hz), 7.42 (1H, t, J=7.7 Hz), 7.06 (1H, br d, J=7.6 Hz), 4.92 (1H, ddd, J=7.6, 7.1, 5.1 Hz), 4.59 (2H, s), 3.78 (3H, s), 2.58 (2H, t, J=7.1 Hz), 2.26 (1H, sm), 2.15 (1H, m), 2.10 (3H, s); ¹³C NMR (CDCl₃) δ 172.59, 166.54, 138.13, 134.25, 131.95, 129.12, 127.42, 126.97, 52.72, 52.14, 45.55, 31.47, 30.12, 15.55.

3545

Step B

(3-(Azidomethyl)benzoyl)-Met-OCH₃

A suspension of (3-(chloromethyl)benzoyl)-Met-OCH₃ (1.58 g, 5.0 mmol) and sodium azide (1.3 g, 20.0 mmol) in DMSO (40 mL) was stirred at 80°C for 7 hours. The mixture was diluted with methylene chloride (100 mL), washed with brine (70 mL x 2) and water (70 mL x 2), and then dried over anhydrous MgSO₄. The solvent was evaporated under reduced pressure to give a yellow residue. Chromatography on silica gel (30% ethyl acetate in hexanes) to provide the desired product (1.45 g) as a colorless solid: m.p. 48-49°C; ¹H NMR (CDCl₃) δ 7.78 (2H, m), 7.49 (2H, m), 6.99 (1H, br d, J=7.4 Hz), 4.49 (1H, ddd, J=7.4, 7.1, 5.2 Hz), 4.42 (2H, s), 3.80 (3H, s), 2.60 (2H, t, J=7.4 Hz), 2.29 (1H, m), 2.17 (1H, m), 2.12 (3H, s); ¹³C NMR (CDCl₃) δ 177.50, 166.54, 135.97, 134.06, 131.18, 128.89, 126.84, 126.71, 54.09, 52.47, 51.95, 31.38, 30.00, 15.30.

Step C

(3-(Aminomethyl)benzoyl)-Met-OCH₃

3560 A suspension of (3-(azidomethyl)benzoyl)-Met-OCH₃ (1.29 g, 4.0 mmol) and 5%
palladium on carbon (0.2 g) in methanol (40 mL) was stirred under a hydrogen atmosphere
(1 atm) for two days at room temperature. The catalyst was removed by filtration through
celite (1.5 g) and the solvent was evaporated in vacuo. The residue was washed with water
(5 mL x 2) and dried to give the desired product (1.12 g) as a colorless foam. ¹H NMR
3565 (CDCl₃) δ 7.81 (1H, s), 7.68 (1H, d, *J*=7.4 Hz), 7.45 (1H, d, *J*=6.5 Hz), 7.36 (1H, t,
J=7.4 Hz), 4.91 (1H, ddd, *J*=7.3, 7.1, 5.1 Hz), 3.90 (2H, s), 3.77 (3H, s), 3.21 (2H, br
s), 2.59 (2H, t, *J*=7.4 Hz), 2.20 (1H, m), 2.12 (1H, m), 2.09 (3H, s).

Compound 2

3570 (4-(Aminomethyl)benzoyl)-Met-OCH₃

The title compound is prepared according to the procedure used to prepare Compound 1 but
replacing 3-(chloromethyl)benzoyl chloride with 4-(chloromethyl)benzoyl chloride.

Compound 3

3575 (3-Aminobenzoyl)-Met-OCH₃

The title compound was prepared according to the procedure described in J. Biol. Chem.
269 12410-12413 (1994).

Compound 4

3580 (4-Aminobenzoyl)-Met-OCH₃

Step A

N-BOC-4-Aminobenzoic acid

4-Aminobenzoic acid (10 g, 72.9 mmol) was placed into a mixture of dioxane (145.8 mL)
3585 and 0.5 M NaOH (145.8 mL). The solution was cooled to 0°C and di-*t*-butyl dicarbonate
(23.87 g, 109.5 mmol) was added. The reaction mixture was allowed to warm to room
temperature and stirred overnight. The next day, the dioxane was removed, the residue was
made acidic and extracted into ethyl acetate. The ethyl acetate fractions were combined and
washed with 1N HCl to remove any unreacted starting material. The solution was dried
3590 over Na₂SO₄ and the solvent was removed in vacuo. The crude material was recrystallized
from ethyl acetate/hexanes to provide the desired product (12.2 g): m.p. 189-190°C; ¹H
NMR (CD₃OD) δ 1.52 (9H, s), 7.49 (2H, d, *J*=8.6 Hz), 7.91 (2H, d, *J*=8.6 Hz), 9.28
(1H, s); ¹³C NMR (CD₃OD) δ 28.59, 81.29, 118.54, 125.30, 131.81, 145.70, 155.00,

169.80; Anal. Calc. for $C_{12}H_{15}NO_4$, C: 60.76, H: 6.37, N: 5.90; Found, C: 60.52, H: 6.43, N: 5.83; HRMS Calc. for $C_{12}H_{15}NO_4$, 237.0961, Found, 237.1001.

Step B

(N-BOC-4-Aminobenzoyl)-Met-OCH₃

Into a dried, nitrogen filled flask was placed N-BOC-4-aminobenzoic acid (8.77 g, 36.97 mmol) in dry methylene chloride (148 mL) along with methionine methyl ester hydrochloride (8.12 g, 40.66 mmol). This solution was cooled in an ice bath and triethylamine (6.7 mL), EDCI (7.80 g, 40.66 mmol) and hydroxybenzotriazole (HOBT, 5.50 g, 40.66 mmol) were added. The mixture was stirred overnight, diluted with more methylene chloride and was extracted three times each with 1 M HCl, 1M NaHCO₃ and water. The methylene chloride was dried over MgSO₄ and the solvent was removed in vacuo. The resulting solid was recrystallized from ethyl acetate/hexanes to yield the desired product (9.72 g): m.p. 184-185°C; ¹H NMR (CDCl₃) δ 1.53 (9H, s), 2.06-2.18 (4H, m), 2.23-2.33 (1H, m), 2.59 (2H, t, *J*=7.6 Hz), 3.80 (3H, s), 4.92 (1H, m), 7.45 (2H, d, *J*=8.7 Hz), 7.77 (2H, d, *J*=8.7 Hz); ¹³C NMR (CDCl₃) δ 15.59, 28.34, 30.15, 31.64, 52.10, 52.73, 81.20, 117.73, 127.8, 128.33, 141.88, 152.33, 166.50, 172.75; Anal. Calc. for $C_{18}H_{26}N_2O_5S$, C: 56.53, H: 6.85, N: 7.29; Found, C: 56.47, H: 6.86, N: 7.29; *m/z* (EI) 382 (M).

Step C

(4-Aminobenzoyl)-Met-OCH₃ hydrochloride

N-BOC-4-aminobenzoyl-Met-OCH₃ (3.53 g, 9.59 mmol) was placed into methylene chloride (30-35 mL) and to it was added 3M HCl/EtO₂ (38.4 mL). After standing, a white precipitate formed. After two hours the solution was decanted and the crystals were collected by centrifugation. The crystals were then washed several times with fresh ether and dried overnight on the vacuum pump. Meanwhile, the filtrate was left to stand overnight to allow additional product to precipitate. The second fraction was washed with ether and dried overnight on the vacuum pump. The total yield of the desired product was 2.87 g: m.p. 158-164°C; ¹H NMR (CDCl₃) δ 2.10 (3H, s), 2.12-2.29 (1H, m), 2.52-2.71 (1H, m), 2.59 (2H, t, *J*=7.6 Hz), 3.75 (3H, s), 4.79 (1H, m), 7.02 (2H, d, *J*=8.6 Hz), 7.55 (2H, d, *J*=8.6 Hz); ¹³C NMR (CDCl₃) δ 15.23, 31.43, 31.53, 52.91, 52.43, 124.35, 130.56, 135.31, 135.76, 168.95, 173.87; HRMS Calc. for $C_{13}H_{18}N_2O_3S$, 282.1038, Found 282.1009.

Compound 5

(4-Amino-3-methylbenzoyl)-Met-OCH₃

Step A

N-BOC-4-Amino-3-methylbenzoic acid

4-Amino-3-methylbenzoic acid (5 g, 33.1 mmol) was reacted according to the same
3635 procedure as that used in the process for preparing N-BOC-4-aminobenzoic acid. The
resulting orange-brown solid was recrystallized from ethyl acetate and hexanes to provide
the desired product (4.99 g) as tan prismatic crystals: m.p. 180-182°C; ¹H NMR (CD₃OD)
d 1.51 (9h, s), 2.27 (3H, s), 7.66 (1H, d, *J*=8.1 Hz), 7.79-7.82 (2H, m), 8.32 (1H, s);
13C NMR (CD₃OD) d 17.98, 28.62, 81.47, 123.12, 127.05, 129.14, 130.65, 132.99,
3640 142.45, 155.33, 168.70; Anal. Calc. for C₁₃H₁₇NO₄, C: 62.15, H: 6.82, N: 5.58; Found
C: 62.07, H: 6.86, N: 5.46; m/z (EI) 251; HRMS Calc. for C₁₃H₁₇NO₄, 251.1158;
Found, 251.1153.

Step B

(N-BOC-4-Amino-3-methylbenzoyl)-Met-OCH₃

N-BOC-4-amino-3-methylbenzoic acid (2.00 g, 7.96 mmol) was reacted with with
methionine methyl ester hydrochloride (1.75 g, 8.76 mmol), triethylamine (1.4 mL), EDCI
(1.68 g, 8.76 mmol) and hydroxybenzotriazole (HOBT, 1.18 g, 8.76 mmol) in dry
methylene chloride (31.8 mL) according to the procedure described for the preparation of N-
3650 BOC-4-aminobenzoyl)-Met-OCH₃. The resulting solid was recrystallized from ethyl
acetate/hexanes to yield the desired product (2.61 g): m.p. 163-165°C; ¹H NMR (CDCl₃) d
1.54 (9H, s), 2.06-2.18 (4H, m), 2.23-2.34 (4H, m), 2.59 (2H, t, *J*=6.8 Hz), 3.80 (3H,
s), 4.92 (1H, m), 6.45 (1H, s), 6.88 (1H, d, *J*=7.5 Hz), 7.63 (1H, d, *J*=8.6 Hz), 7.66
(1H, s), 8.05 (1H, d, *J*=8.6 Hz); ¹³C NMR (CDCl₃) d 15.47, 17.61, 28.22, 30.03,
3655 31.55, 51.93, 52.57, 81.04, 118.73, 125.62, 127.66, 129.54, 139.89, 152.34, 166.58,
172.66.

Step C

(4-Amino-3-methylbenzoyl)-Met-OCH₃ hydrochloride

N-BOC-4-Amino-3-methylbenzoyl-Met-OCH₃ (0.99 g, 2.59 mmol) was dissolved in
methylene chloride (15-20 mL) and precipitated with 3M HCl/Et₂O (20.7 mL). A pale
orange precipitate was obtained, washed with ether and dried overnight on the vacuum
pump. The total yield of the desired product was 0.83 g: m.p. 157-159°C; ¹H NMR
(CD₃OD) d 2.04 (3H, s), 2.11-2.25 (1H, m), 2.47 (3H, s), 2.52-2.68 (3H, m), 3.74 (3H,
3665 s), 4.75-4.80 (1H, m), 7.48 (1H, d, *J*=8.2 Hz), 7.81 (2H, d, *J*=8.2 Hz), 7.87 (1H, s);
¹³C NMR (CD₃OD) d 15.23, 17.28, 31.43, 31.51, 52.91, 53.37, 124.41, 127.85,

131.99, 133.63, 134.14, 135.65, 169.05, 173.84; Anal. Calc. for $C_{14}H_{21}N_2O_3S$, C: 50.52, H: 6.36, N: 8.42; Found C: 50.71, H: 6.40, N: 8.34.

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Compound 6

(4-Amino-3-methoxybenzoyl)-Met-OCH₃

Step A

N-BOC-4-Amino-3-methoxybenzoic acid

3675 4-Amino-3-methoxybenzoic acid (1 g, 5.98 mmol) was reacted according to the same procedure as that used in the process for preparing N-BOC-4-aminobenzoic acid. The resulting solid was recrystallized from ethyl acetate and hexanes to provide the desired product (1.5 g) as tan crystals: m.p. 176-178°C; ¹H NMR (CD₃OD) δ 1.52 (9H, s), 3.92 (3H, s), 7.56 (1H, s), 7.62 (1H, d, *J*=8.4 Hz), 7.96 (1H, s), 8.03 (1H, d, *J*=8.4 Hz); ¹³C NMR (CD₃OD) δ 28.53, 56.35, 81.78, 112.01, 118.58, 124.20, 125.76, 133.84, 149.04, 154.20, 169.60; HRMS Calc. for $C_{13}H_{17}NO_5$, 267.1107; Found, 267.1103.

3680

Step B

(N-BOC-4-Amino-3-methoxybenzoyl)-Met-OCH₃

3685 N-BOC-4-amino-3-methoxybenzoic acid (0.35 g, 1.31 mmol) was reacted with with methionine methyl ester hydrochloride (0.9 g, 1.43 mmol) using EDCI according to the procedure described for the preparation of (N-BOC-4-aminobenzoyl)-Met-OCH₃. The resulting solid was recrystallized from ethyl acetate/hexanes to yield the desired product (0.36 g): m.p. 163-165°C; ¹H NMR (CDCl₃) δ 1.53 (9H, s), 2.09-2.18 (4H, m), 2.23-2.35 (1H, m), 2.60 (2H, t, *J*=6.9 Hz), 3.80 (3H, s), 3.93 (3H, s), 4.92 (1H, br s), 6.93 (1H, d, *J*=7.6 Hz), 7.25 (1H, m), 7.31 (1H, d, *J*=10.2 Hz), 7.44 (1H, s), 8.15 (1H, d, *J*=8.5 Hz); ¹³C NMR (CDCl₃) δ 15.47, 28.23, 30.09, 31.48, 52.06, 52.54, 55.81, 80.82, 98.06, 109.38, 116.66, 119.31, 131.52, 147.23, 152.31, 166.57, 172.58; *m/z* (FAB) 413 (*M* + 1).

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Step C

(4-Amino-3-methoxybenzoyl)-Met-OCH₃ hydrochloride

N-BOC-4-Amino-3-methoxybenzoyl-Met-OCH₃ (0.71 g, 1.79 mmol) was dissolved in methylene chloride (4 mL) and precipitated with 3M HCl/Et₂O (12 mL). A reddish precipitate was obtained, washed with ether and dried overnight on the vacuum pump. The total yield of the desired product was 0.55 g: m.p. 176-177°C; ¹H NMR (CD₃OD) δ 2.08 (3H, s), 2.21 (2H, m), 2.61 (2H, m), 3.74 (3H, s), 4.02 (3H, s), 4.79 (1H, m), 7.50

3700

(1H, d, $J=8.2$ Hz), 7.57 (1H, d, $J=4.1$ Hz), 7.67 (1H, s); ^{13}C NMR (CD_3OD) δ 15.26, 31.34, 31.42, 52.95, 53.38, 57.12, 112.29, 121.43, 124.57, 124.77, 136.15, 153.67, 168.79, 173.81.

Compound 7

(4-Amino-1-naphthoyl)-Met-OCH₃

Step A

4-Amino-1-naphthoic acid

4-Amino-1-naphthalenecarbonitrile (1.5 g, 8.91 mmol) was suspended in a 50% KOH solution (18 mL). The heterogeneous solution was heated at reflux for 2-3 days. Once the solution became homogeneous and TLC showed no more starting material, the deep red solution was cooled and poured over 200 mL of water. The resulting solution was then filtered and the desired product was precipitated with concentrated HCl. The resulting red crystals were filtered and the filtrate was refiltered to give pink crystals. The first fraction of crystals was treated with activated carbon to remove some of the red color. A total of 1.51 g of the desired product was obtained: m.p. 169-171°C; ^1H NMR (CD_3OD) δ 6.69 (1H, d, $J=8.2$ Hz), 7.38-7.43 (1H, m), 7.48-7.54 (1H, m), 8.03 (1H, d, $J=8.5$ Hz), 8.13 (1H, d, $J=8.2$ Hz), 9.09 (1H, d, $J=8.5$ Hz); ^{13}C NMR (CD_3OD) δ 107.39, 114.61, 122.99, 123.92, 125.21, 127.40, 128.48, 135.04, 151.35, 171.44; HRMS Calc. for $\text{C}_{11}\text{H}_7\text{NO}_2$, 187.0633; Found, 187.0642.

Step B

N-BOC-4-Amino-1-naphthoic acid

4-Amino-1-naphthoic acid (0.86 g, 4.61 mmol) was dissolved in dioxane (9.2 mL). Di-*t*-butyl dicarbonate (1.11 g, 5.07 mmol) was added and the mixture was stirred overnight. The reaction mixture was worked up as described above for N-BOC-4-aminobenzoic acid to give 0.76 g of the desired product as a reddish pink solid: m.p. 194-195°C; ^1H NMR (CD_3OD) δ 1.56 (9H, s), 7.53-7.62 (2H, m), 7.79 (1H, d, $J=8.1$ Hz), 8.12 (1H, d, $J=8.0$ Hz), 8.22 (1H, d, $J=8.18$ Hz), 9.02 (1H, d, $J=8.9$ Hz); ^{13}C NMR (CD_3OD) δ 26.68, 81.62, 119.06, 123.40, 124.57, 127.03, 127.37, 128.49, 128.77, 131.89, 133.76, 139.86, 155.95, 170.73; Anal. Calc. for $\text{C}_{17}\text{H}_{17}\text{NO}_4$, C: 66.90, H: 5.96, N: 4.88; Found C: 66.49, H: 6.08, N: 4.79; m/z (EI), 289; HRMS Calc. for $\text{C}_{16}\text{H}_{17}\text{NO}_4$, 287.1158; Found, 287.1151.

Step C

(N-BOC-4-Amino-1-naphthoyl)-Met-OCH₃

- 3740 N-BOC-4-Amino-naphthoic acid (0.46 g, 1.60 mmol), methionine methyl ester hydrochloride (0.35 g, 1.76 mmol), EDCI (0.43 g, 1.76 mmol), HOBT (0.24 g, 1.76 mmol) and triethylamine (0.27 mL) in methylene chloride (6.4 mL) were reacted as described above for N-BOC-4-aminobenzoyl-Met-OCH₃. After workup and recrystallization from ethyl acetate hexanes, the desired product (0.44 g) was obtained as
- 3745 pale pink crystals: m.p. 131-132°C; ¹H NMR (CDCl₃) δ 1.57 (9H, s), 2.11-2.21 (4H, m), 2.29-2.41 (1H, m), 2.65 (2H, t, *J*=7.1 Hz), 3.83 (3H, s), 4.99-5.06 (1H, m), 6.68 (1H, d, *J*=8.0 Hz), 7.02 (1H, s), 7.56-7.59 (2H, m) 7.69 (1H, d, *J*=7.9 Hz), 7.87-7.90 (1H, m), 8.02 (1H, d, *J*=7.9 Hz), 8.44-8.48 (1H, m); ¹³C NMR (CDCl₃) δ 15.56, 28.31, 30.19, 31.65, 52.06, 52.64, 81.17, 115.82, 120.18, 125.79, 126.37, 126.53,
- 3750 127.18, 131.02, 135.65, 152.93, 169.04, 172.40; HRMS Calc. for C₂₂H₂₈N₂O₅S, 432.1719; Found, 432.1702; *m/z* (FAB) 433 (*M*+1).

Step D(4-Amino-1-naphthoyl)-Met-OCH₃ hydrochloride

- 3755 (N-BOC-4-Amino-1-naphthoyl)-Met-OCH₃ (0.57 g, 1.31 mmol) was deprotected with HCl/ether to yield the desired product (0.31 g) as a white solid: m.p. 178-181°C; ¹H NMR (CD₃OD) δ 2.08-2.16 (4H, m), 2.20-2.30 (1H, m) 2.57-2.75 (2H, m) 3.82 (3H, s), 4.87-4.91 (1H, m), 7.59 (1H, d, *J*=7.5 Hz), 7.67 (1H, d, *J*=7.5 Hz) 7.71-7.80 (2H, m), 8.03 (1H, dd, *J*=7.1, 2.0 Hz), 8.35 (1H, dd, *J*=6.8, 1.8 Hz); ¹³C NMR (CD₃OD) δ 15.23,
- 3760 31.40, 53.01, 53.33, 119.90, 122.20, 126.15, 127.41, 127.77, 129.09, 129.31, 131.50, 132.33, 135.64, 171.77, 173.83; *m/z* (FAB), 369 (*M*+1).

Compound 8(4-Amino-2-phenylbenzoyl)-Met-OCH₃

3765

Step A4-Nitro-2-phenyltoluene

- 2-Bromo-4-nitrotoluene (2.16 g, 10.00 mmol) and phenylboric acid (1.46 g, 12.00 mmol) were dissolved in anhydrous DMF (25 mL) under nitrogen. To this mixture was added
- 3770 Pd(Ph₃P)₄ (0.58 g, 5%). The mixture was heated at 100°C overnight. The solution was poured onto 1N HCl and extracted with Et₂O. The crude product was chromatographed on silica gel using hexanes as eluent. After recrystallization from ethanol, the desired product (1.23 g) was obtained as pale orange needles: m.p. 69-71°C; ¹H NMR (CDCl₃) δ 2.36 (3H, s), 7.29-7.40 (2H, m), 7.41-7.49 (5H, m), 8.07-8.10 (2H, m); ¹³C NMR (CDCl₃)

3775 d 20.68, 121.96, 124.51, 127.78, 128.41, 128.83, 131.06, 139.06, 139.44, 142.97, 143.48, 146.05; Anal. Calc. for $C_{13}H_{11}NO_2$, C: 73.26, H: 5.20, N: 6.57; Found, C: 73.10, H: 5.12, N: 6.50; m/z (EI) 213; HRMS Calc. for $C_{13}H_{11}NO_2$, 213.0790; Found, 213.0793.

3780

Step B

4-Nitro-2-phenylbenzoic acid

4-Nitro-2-phenyltoluene (0.5 g, 2.34 mmol) was dissolved in water (4.6 mL) and pyridine (2.3 mL). The mixture was heated to reflux and $KMnO_4$ (1.85 g, 11.7 mmol) was added. The reaction mixture was heated overnight and the solution was filtered and washed several
3785 times with boiling water. The aqueous solution was made acidic and the product was extracted into ethyl acetate. The ethyl acetate solution was dried over Na_2SO_4 and the solvent removed in vacuo to provide the desired product (0.37 g): m.p. 174-176°C, 1H NMR (CD_3OD) d 7.38-7.48 (5H, m), 7.96 (1H, d, $J=8.5$ Hz), 8.21 (1H, d, $J=2.3$ Hz), 8.28 (1H, dd, $J=8.48, 2.37$ Hz); ^{13}C NMR (CD_3OD) d 122.95, 126.09, 129.27, 129.42,
3790 129.49, 131.56, 139.26, 140.42, 144.41, 150.17, 170.52; m/z (EI) 243 (M).

Step C

(4-Nitro-2-phenylbenzoyl)-Met-OCH₃

4-Nitro-2-phenylbenzoic acid (0.3 g, 1.23 mmol), methionine methyl ester hydrochloride
3795 salt (0.27 g, 1.35 mmol), EDCI (0.26 g, 1.35 mmol), HOBT (0.18 g, 1.35 mmol) and triethylamine (0.19 mL) in dry methylene chloride (4.9 mL) were reacted according the procedure described above for (N-BOC-4-aminobenzoyl)-Met-OCH₃. After recrystallization of the product from ethyl acetate hexanes, the desired product (0.41 g) was obtained: m.p. 98-101°C; 1H NMR ($CDCl_3$) d 1.62-1.73 (1H, m), 1.79-1.88 (1H, m),
3800 1.91 (3H, s), 1.99 (2H, t, $J=7.2$ Hz), 3.59 (3H, s), 4.53 (1H, m), 6.45 (1H, d, $J=7.8$ Hz), 7.33-7.40 (5H, m), 7.67 (1H, d, $J=8.3$ Hz), 8.07-8.12 (2H, m); ^{13}C NMR ($CDCl_3$) d 14.92, 29.11, 30.67, 51.51, 52.29, 121.86, 124.74, 128.27, 128.60, 128.69, 129.52, 137.50, 140.56, 141.02, 148.09, 167.23, 171.23; m/z (FAB), 389 (M+1).

3805

Step D

(4-Amino-2-phenylbenzoyl)-Met-OCH₃

(4-Nitro-2-phenylbenzoyl)-Met-OCH₃ (0.35 g, 0.90 mmol) was dissolved in ethyl acetate (9.0 mL). To this mixture was added $SnCl_2 \cdot 2H_2O$ (1.02 g, 4.5 mmol) and the reaction
3810 mixture was heated under nitrogen at reflux for one hour. The mixture was poured onto ice, the solution was made basic using $NaHCO_3$ and the product was extracted into ethyl acetate several times (7-8). The ethyl acetate solutions were combined, washed with brine and

dried over Na₂SO₄. The solvent was removed in vacuo to the desired product (0.24 g) as a yellow solid: ¹H NMR (CDCl₃) δ 1.58-1.70 (1H, m), 1.80-1.92 (1H, m), 1.98 (3H, s), 2.06 (2H, t, J=7.7 Hz), 3.62 (3H, s), 4.00 (2H, br s), 4.56-4.63 (1H, m), 5.84 (1H, d, J=7.7 Hz), 6.50 (1H, s), 6.61 (1H, d, J=8.4 Hz) 7.29-7.42 (5H, m), 7.58 (1H, d, J=8.3 Hz); ¹³C NMR (CDCl₃) δ 15.02, 29.25, 31.25, 51.57, 52.15, 113.27, 115.88, 123.52, 127.56, 128.37, 128.44, 130.92, 140.66, 141.44, 148.53, 168.58, 171.91.

Compound 9

3820

(4-Amino-2-(2-thienyl)benzoyl)-Met-OCH₃

The title compound can be prepared according to the method used to prepare Compound 8, only substituting thiophene-2-boronic acid for phenyl boronic acid.

Compound 10

3825

(4-Amino-2-(1-naphthyl)benzoyl)-Met-OCH₃

The title compound can be prepared according to the method used to prepare Compound 8, only substituting 1-naphthylboronic acid for phenylboronic acid.

Compound 11

3830

4-Amino-3'-methylbiphenyl

The title compound was prepared by Suzuki coupling of 1-bromo-4-nitrobenzene and 1-bromo-3-methylbenzene.

Compound 12

3835

4-Amino-4'-biphenyl carboxylic acid

Step A

4-Nitro-4'-methylbiphenyl

The title compound was prepared by Suzuki coupling of 1-bromo-4-nitrobenzene and 1-bromo-4-methylbenzene.

Step B

4-Nitro-4'-biphenyl carboxylic acid

The title compound was prepared by KMnO₄ oxidation of 4-nitro-4'-methylbiphenyl.

3845

Step C

4-Amino-4'-biphenyl carboxylic acid

The title compound can be prepared by palladium catalyzed hydrogenation of 4-nitro-4'-biphenyl carboxylic acid.

3850

Compound 13

4-Amino-3'-biphenyl carboxylic acid

Step A

3855

4-Nitro-3'-methylbiphenyl

The title compound was prepared by Suzuki coupling of 1-bromo-4-nitrobenzene and 1-bromo-3-methylbenzene.

Step B

3860

4-Nitro-3'-biphenyl carboxylic acid

The title compound was prepared by KMnO_4 oxidation of 4-nitro-3'-methylbiphenyl.

Step C

4-Amino-3'-biphenyl carboxylic acid

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The title compound can be prepared by palladium catalyzed hydrogenation of 4-nitro-3'-biphenyl carboxylic acid.

Compound 14

4-Amino-2-methoxy-3'-biphenyl carboxylic acid

3870

Step A

2-Methoxy-4-nitro-3'-methylbiphenyl

The title compound was prepared by reaction of 1-bromo-2-methoxy-4-nitrobenzene with 3-methylphenylboronic acid in the presence of palladium acetate.

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Step B

2-Methoxy-4-nitro-3'-biphenylcarboxylic acid

The title compound was prepared by KMnO_4 oxidation of 2-methoxy-4-nitro-3'-methylbiphenyl.

3880

Step C

4-Amino-2-methoxy-3'-biphenyl carboxylic acid

The title compound can be prepared by palladium catalyzed hydrogenation of 2-methoxy-4-nitro-3'-biphenyl carboxylic acid.

3885

Compound 154-Amino-2-isopropoxy-3'-biphenyl carboxylic acid

The title compound can be prepared by methods analogous to those used to prepare Compound 14.

3890

Compound 164-Amino-2-phenyl-3'-biphenylcarboxylic acid

The title compound can be prepared by methods analogous to those used to prepare Compound 14.

3895

Compound 17(4-Amino-2-(3,5-dimethylphenyl)benzoyl)-Met-OCH₃Step A

3900

2-Bromo-4-nitrobenzoic acid

2-Bromo-4-nitrotoluene (5.0 g, 23.14 mmol) was dissolved in pyridine (23 mL) and water (46 mL). The heterogeneous mixture was heated to 60°C and KMnO₄ (18.29 g, 115.7 mmol) was added carefully. The mixture was then heated under reflux overnight. The reaction mixture was filtered and washed with boiling water. The solution was then made acidic and extracted into ethyl acetate, dried over Na₂SO₄ and the solvent was removed in vacuo. The crude product was dissolved in aqueous NaOH and washed with hexanes. The aqueous phase was made acidic and the product was extracted into ethyl acetate. The ethyl acetate solutions were combined and dried over Na₂SO₄ and the solvent was removed in vacuo to provide the desired product (3.72 g): m.p. 158-160°C; ¹H NMR (CD₃OD) δ 7.81 (1H, d, J=8.5 Hz), 8.08 (1H, d, J=8.5 Hz), 8.30 (1H, s); ¹³C NMR (CD₃OD) δ 121.96, 122.75, 129.36, 132.24, 139.52, 149.54, 167.75; Anal. Calc. for C₇H₄BrNO₄ • 0.1 ethyl acetate, C: 34.88, H: 1.90, N: 5.50; Found, C: 34.68, H: 1.86, N: 5.82.

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3910

Step B

3915

3,5-Dimethylphenylboronic acid

Magnesium turnings (1.44 g, 59.43 mmol) were covered with dry THF (18.8 mL) in a dried, nitrogen filled flask fitted with an addition funnel and reflux condenser. To this was added 5-bromo-m-xylene (10 g, 54.03 mmol) in THF (15 mL) after initiation of the Grignard reaction. The addition was carried out over several minutes and the reaction mixture was heated at reflux for 1-2 hours until most of the magnesium had reacted. The reaction mixture was then cooled and transferred to an addition funnel fitted to an nitrogen

3920

filled flask containing triisopropyl borate (24.9 mL) at -70°C. The dropwise addition was carried out over several minutes and the mixture warmed to room temperature and stirred overnight. The grey solution was poured onto 2 M HCl and immediately turned yellow.
3925 The solution was extracted with Et₂O and the Et₂O fractions were combined, dried over MgSO₄ and the solvent was removed in vacuo to provide the desired product (2.41 g): m.p.249-251°C; ¹H NMR (CDCl₃) δ 2.44 (6H, s), 7.23 (1H, s), 7.84 (2H, s); ¹³C NMR (CD₃OD) δ 21.36, 133.28, 134.39, 137.48.

3930

Step C4-Nitro-2-(3,5-dimethylphenyl)benzoic acid

2-Bromo-4-nitrobenzoic acid (0.43 g, 2.03 mmol) and 3,5-dimethylphenyl boronic acid (0.334 g, 2.23 mmol) were dissolved in anhydrous DMF (25 mL) under nitrogen. To this mixture was added Cs₂CO₃ (1.66 g, 5.08 mmol) followed by Pd(Ph₃P)₄ (0.12 g, 5%).

3935 The mixture was heated at 100°C overnight. The solution was poured onto 1N HCl and extracted with Et₂O. It was dried over MgSO₄ and the solvent was removed in vacuo. The crude product was chromatographed on silica gel using a 9:1 mixture of hexanes and ethyl acetate to provide the desired product (0.34 g): ¹H NMR (CDCl₃) δ 2.36 (6H, s), 6.99 (2H, s), 7.07 (1H, s), 8.03 (1H, d, J=9.0 Hz), 8.23-8.25 (2H, m); ¹³C NMR (CDCl₃) δ
3940 21.28, 121.68, 123.68, 125.74, 126.07, 130.22, 131.19, 131.31, 135.04, 138.21, 144.74, 170.75.

Step D(4-Nitro-2-(3,5-dimethylphenyl)benzoyl)-Met-OCH₃

3945 4-Nitro-2-(3,5-dimethylphenyl)benzoic acid (0.15 g, 0.55 mmol), methionine methyl ester hydrochloride (0.11 g, 0.55 mmol), EDCI (0.11 g, 0.55 mmol), HOBT (0.07 g, 0.55 mmol) and triethylamine (0.08 mL) in dry methylene chloride (2.2 mL) were reacted and worked up according to the procedure for (N-BOC-4-aminobenzoyl)-Met-OCH₃ as described above. After recrystallization from ethyl acetate and hexanes, the desired product
3950 was obtained (0.13 g): m.p. 122-124°C; ¹H NMR (CDCl₃) δ 1.2-1.84 (1H, m), 1.85-1.97 (1H, m), 2.01 (3H, s), 2.05 (3H, t, J=7.7Hz), 2.38 (6H, s), 3.70 (3H, s), 4.67-4.74 (1H, m), 6.03 (1H, d, J=7.9 Hz), 7.05 (2H, s), 7.09 (1H, s), 7.84-7.87 (1H, m), 7.84-7.87 (1H, m) 8.23-8.26 (2H, m); ¹³C NMR (CDCl₃) δ 15.20, 21.26, 29.22, 31.15, 51.79, 52.57, 122.07, 125.11, 126.27, 130.03, 130.53, 137.77, 138.82, 140.29, 141.56,
3955 148.41, 167.14, 171.53.

Step E(4-Amino-2-(3,5-dimethylphenyl)benzoyl)-Met-OCH₃

3960 (4-Nitro-2-(3,5-dimethylphenyl)benzoyl)-Met-OCH₃ (0.11 g, 0.26 mmol) was dissolved in ethyl acetate (3.0 mL). To this mixture was added SnCl₂ · 2H₂O (0.3 g, 1.30 mmol) and the reaction was heated under nitrogen at reflux for 6 hours. The mixture was worked up as described above for (4-amino-2-phenylbenzoyl)-Met-OCH₃ to give the desired product (0.15 g): ¹H NMR (CDCl₃) δ 1.60-1.70 (1H, m), 1.80-1.90 (1H, m), 1.99 (3H, s), 2.05 (2H, t, *J*=7.6 Hz), 2.33 (6H, s), 3.64 (3H, s), 3.93 (2H, br s), 4.61-4.64 (1H, m), 5.82 (1H, d, *J*=7.7 Hz), 6.49 (1H, d, *J*=2.3 Hz), 6.62 (1H, dd, *J*=8.4, 2.4 Hz), 6.98 (2H, s), 7.00 (1H, s), 7.65 (1H, d, *J*=8.3 Hz); ¹³C NMR (CDCl₃) δ 15.08, 21.17, 29.28, 31.49, 51.70, 52.18, 113.30, 115.94, 123.55, 126.36, 129.32, 131.23, 138.15, 140.72, 141.92, 148.40, 168.45, 172.01.

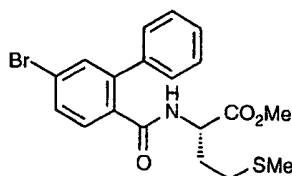
3970

Preparation 1

Anilines of the formula B-NH₂

The anilines from Table 1, entries 10-126 (B-NH₂) are prepared using the procedures for Compounds 1-18 with the exception that methionine methyl ester is replaced by methioninesulfone methyl ester, (S-Me)cysteine methyl ester, serine methyl ester, (O-Me)serine methyl ester, (O-Me)homoserine methyl ester, homoserine lactone, isoleucine methyl ester, leucine methyl ester, norleucine methyl ester, norvaline methyl ester, cyclohexylalanine methyl ester, phenylalanine methyl ester, or glutamic acid dimethyl ester.

3980



Preparation 2

4-Bromo-2-phenylbenzoyl methionine methyl ester

Preparation 2A

3985

4-Bromo-2-phenylbenzoic acid methyl ester

A solution of methyl 4-amino-2-phenylbenzoic acid (1.0 equivalent) in dilute aqueous HBr is treated with NaNO₂ (1.1 equivalents) to form the diazonium salt. The reaction is treated with CuBr (1.1 equivalents) and heated. When judged complete by TLC analysis, the mixture is extracted into ethyl acetate which is dried and evaporated. The title arylbromide is purified by chromatography on silica gel.

3990

Preparation 2B4-Bromo-2-phenylbenzoic acid

3995 To a solution of the resultant compound from Preparation 2A (1.0 equivalent) in a 3:1 mixture of tetrahydrofuran (THF) and water is added an excess (1.5 equivalents) of LiOH. When hydrolysis is judged complete by TLC analysis, the solvent is evaporated and the remaining aqueous layer is acidified to pH = 3 and extracted into ethyl acetate which is dried and evaporated prior to purification by chromatography on silica gel.

4000

Preparation 2C4-Bromo-2-phenylbenzoyl methionine methyl ester

4005 To a solution of the resultant compound from Preparation 2B (1.0 equivalent) in dimethylformamide (DMF) is added 3-hydroxy-1,2,3-benzotriazin-4(3H)-one (1.5 equivalents) followed by methionine methyl ester (1.0 equivalent) and 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (1.5 equivalents). When judged complete by TLC analysis, the reaction is taken up in ethyl acetate which is washed by 1N HCl and saturated brine, and then is dried and evaporated. The crude reaction mixture is purified by column chromatography to afford the title product.

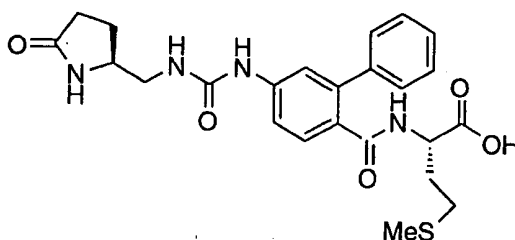
4010

Preparation 2D4-Bromo-2-phenylbenzoyl methionine methyl ester alternate procedure

4015 A solution of 4-amino-2-phenylbenzoyl methionine methyl ester (1.0 equivalent) in dilute aqueous HBr is treated with NaNO₂ (1.1 equivalents) to form the diazonium salt. The reaction is treated with CuBr (1.1 equivalents) and heated. When judged complete by TLC analysis, the mixture is extracted into ethyl acetate which is dried and evaporated. The title arylbromide is purified by chromatography on silica gel.

Preparation 3Arylbromides of the formula B-Br

4020 The anilines from Table 1 (B-NH₂) are reacted according to the procedures of Preparation 2 to provide the arylbromides listed in Table 2.



4025

Example 14-((S)-2-Pyrrolidone-5-aminomethylcarbonyl)amino-2-phenylbenzoyl methionineExample 1AMethyl 4-((S)-2-Pyrrolidone-5-aminomethylcarbonyl)amino-2-phenylbenzoate

4030 To a solution of methyl 4-amino-2-phenylbenzoate hydrochloride (1.0 equivalent) in toluene is added triphosgene (0.33 equivalent) and the mixture is heated at reflux until judged complete by TLC analysis. The intermediate is reacted without further purification with (S)-5-aminomethyl-2-pyrrolidone (1.0 equivalent) and triethylamine (2.0 equivalents). When judged complete by TLC analysis, the reaction is taken up in ethyl acetate and washed with
4035 1N HCl and brine, evaporated, and purified by chromatography on silica gel.

Example 1B4-((S)-2-Pyrrolidone-5-aminomethylcarbonyl)amino-2-phenylbenzoic acid

4040 To a solution of the resultant compound from Example 1A (1.0 equivalent) in a 3:1 mixture of tetrahydrofuran (THF) and water is added an excess (1.5 equivalents) of LiOH. When hydrolysis is judged complete by TLC analysis, the solvent is evaporated and the remaining aqueous layer is acidified to pH = 3 and extracted into ethyl acetate which is dried and evaporated prior to purification by chromatography on silica gel.

4045

Example 1C4-((S)-2-Pyrrolidone-5-aminomethylcarbonyl)amino-2-phenylbenzoyl methionine methyl ester

To a solution of the resultant compound from Example 1B (1.0 equivalent) in dimethylformamide (DMF) is added 3-hydroxy-1,2,3-benzotriazin-4(3H)-one (1.5
4050 equivalents) followed by methionine methyl ester (1.0 equivalent) and 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (1.5 equivalents). When judged complete by TLC analysis, the reaction is taken up in ethyl acetate which is washed with 1N HCl and saturated brine, and then is dried and evaporated. The crude reaction mixture is purified by column chromatography to afford the title product.

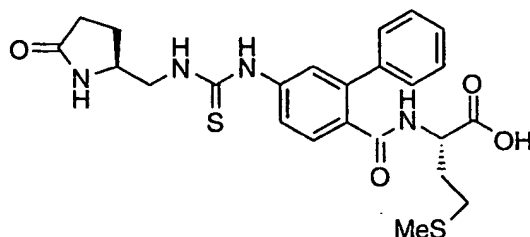
4055

Example 1D4-((S)-2-Pyrrolidone-5-aminomethylcarbonyl)amino-2-phenylbenzoyl methionine methyl ester, alternate preparation

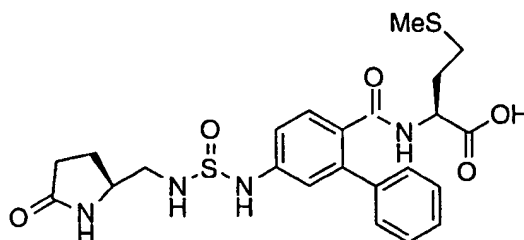
To a solution of 4-amino-2-phenylbenzoyl methionine methyl ester (1.0 equivalent) in methylene chloride is added a solution of phosgene in toluene (1.0 equivalent) and triethylamine (2.0 equivalents). The intermediate is reacted without further purification with (S)-5-aminomethyl-2-pyrrolidone (1.0 equivalent) and triethylamine (1.0 equivalent). When judged complete by TLC analysis, the reaction is taken up in ethyl acetate and washed with 1N HCl and brine, evaporated, and purified by chromatography on silica gel.

Example 1E4-((S)-2-Pyrrolidone-5-aminomethylcarbonyl)amino-2-phenylbenzoyl methionine

To a solution of the resultant compound from Example 1C in a 3:1 mixture of THF and water is added an excess of LiOH (1.5 equivalents). When hydrolysis is judged complete by TLC analysis, the solvent is evaporated and the remaining aqueous layer is acidified to pH = 3 and extracted into ethyl acetate which is dried and evaporated prior to purification by chromatography on silica gel.

Example 24-((S)-2-Pyrrolidone-5-aminomethylthiocarbonyl)amino-2-phenylbenzoyl methionine

The title compound is prepared as described in Example 1 with the exception that triphosgene (0.33 equivalent) is replaced by thiophosgene (1.0 equivalent).

Example 3

4-((S)-2-Pyrrolidone-5-aminomethylsulfinyl)amino-2-phenylbenzoyl methionine

4085

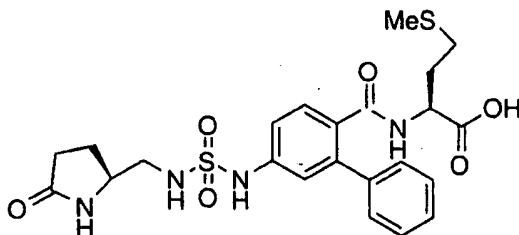
Example 3A4-((S)-2-Pyrrolidone-5-aminomethylsulfinyl)amino-2-phenylbenzoyl methionine methyl ester

To a solution of 4-amino-2-phenylbenzoyl methionine methyl ester (1.0 equivalent) in methylene chloride is added thionyl chloride (1.0 equivalent) and triethylamine (2.0 equivalents). After the amine has fully reacted, (S)-5-aminomethyl-2-pyrrolidone (1.0 equivalent) is added. When the reaction is judged complete by TLC analysis, the product is isolated as described in Example 1A and purified by chromatography on silica gel.

4095

Example 3B4-((S)-2-Pyrrolidone-5-aminomethylsulfinyl)amino-2-phenylbenzoyl methionine

To a solution of the resultant compound from Example 3A in a 3:1 mixture of THF and water is added an excess of LiOH (1.5 equivalents). When hydrolysis is judged complete by TLC analysis, the solvent is evaporated and the remaining aqueous layer is acidified to pH = 3 and extracted into ethyl acetate which is dried and evaporated prior to purification by chromatography on silica gel.



4105

Example 44-((S)-2-Pyrrolidone-5-aminomethylsulfonyl)amino-2-phenylbenzoyl methionineExample 4A4-((S)-2-Pyrrolidone-5-aminomethylsulfonyl)amino-2-phenylbenzoyl methionine methyl ester

4110

To a solution of 4-amino-2-phenylbenzoyl methionine methyl ester (1.0 equivalent) in methylene chloride is added sulfonyl chloride (1.0 equivalent) and triethylamine (2.0 equivalents). After the amine has fully reacted, (S)-5-aminomethyl-2-pyrrolidone (1.0 equivalent) is added. When the reaction is judged complete by TLC analysis, the product is isolated as described in Example 1A and purified by chromatography on silica gel.

4115

Example 4B4-((S)-2-Pyrrolidone-5-aminomethylsulfonyl)amino-2-phenylbenzoyl methionine methyl ester, alternate procedure

4120 A solution of 1 equivalent of 4-amino-2-phenylbenzoyl methionine methyl ester (1.0 equivalent) and sulfonyl chloride (1.0 equivalent) in acetonitrile with a catalytic amount of antimony(V) chloride is heated to reflux until judged complete by TLC analysis. The solution is then cooled, filtered, and all volatiles are removed under reduced pressure. The residue is taken up in dichloromethane and treated with triethylamine (1 equivalent and (S)-

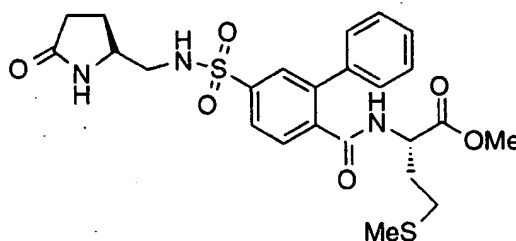
4125 5-aminomethyl-2-pyrrolidone (1.0 equivalent). When the reaction is judged complete by TLC analysis, the product is isolated as described in Example 1A and purified by chromatography on silica gel.

Example 4C

4130 4-((S)-2-Pyrrolidone-5-aminomethylsulfonyl)amino-2-phenylbenzoyl methionine methyl ester

The resultant compound from Example 4A is hydrolyzed according to the procedure of Example 1B to give the title product.

4135

Example 54-((S)-2-Pyrrolidone-5-methylaminosulfonyl)-2-phenylbenzoyl methionine

4140

Example 5A4-Chlorosulfonyl-2-phenylbenzoic acid methyl ester

To a solution of methyl 4-amino-2-phenylbenzoate (1.0 equivalent) in concentrated HCl is added a solution of sodium nitrite (1.1 equivalents) until an excess of nitrous acid persists. The chlorodiazonium salt is poured into a solution of sulfur dioxide (10 equivalents), copper

4145 (II) chloride (0.5 equivalent) and KCl (1.1 equivalents) in dioxane. When TLC analysis indicated that the reaction is complete, the mixture is diluted with water and extracted into benzene which is dried and evaporated to give the title sulfonyl chloride

Example 5B

4150 4-((S)-2-Pyrrolidone-5-aminomethyl)sulfonyl)-2-phenylbenzoic acid methyl ester
To a solution of the resultant compound from Example 5A (1.0 equivalent) in methylene chloride is added (S)-5-aminomethyl-2-pyrrolidone (1.0 equivalent) and triethylamine (1.0 equivalent). When the reaction is judged complete by TLC analysis, the solvent is evaporated and the residue is purified by chromatography on silica gel.

4155

Example 5C4-((S)-2-Pyrrolidone-5-aminomethyl)sulfonyl)-2-phenylbenzoic acid

The resultant compound from Example 5B is hydrolyzed according to the procedure of Example 1B to give the title product.

4160

Example 5D4-((S)-2-Pyrrolidone-5-aminomethyl)sulfonyl)-2-phenylbenzoyl methionine methyl ester

To a solution of the resultant compound from Example 5C (1.0 equivalent) in (DMF) is added 3-hydroxy-1,2,3-benzotriazin-4(3H)-one (1.5 equivalents) followed by methionine methyl ester (1.0 equivalent) and 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (1.5 equivalents). When judged complete by TLC analysis, the reaction is taken up in ethyl acetate which is washed by 1N HCl and saturated brine, and then is dried and evaporated. The crude reaction mixture is purified by column chromatography to afford the title product.

4170

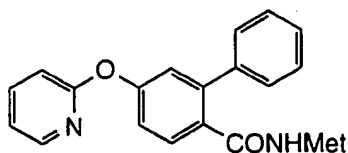
Example 5E4-((S)-2-Pyrrolidone-5-aminomethylcarbonyl)amino-2-phenylbenzoyl methionine methyl ester, alternate preparation

4175 To a solution of 4-amino-2-phenylbenzoyl methionine methyl ester (1.0 equivalent) in concentrated HCl is added a solution of sodium nitrite (1.1 equivalents) until an excess of nitrous acid persists at which time the chlorodiazonium salt will be treated with gaseous sulfur dioxide and copper (II) chloride to give the sulfonyl chloride (0.1 equivalent). This intermediate is reacted with (S)-5-aminomethyl-2-pyrrolidone (1.0 equivalent) and triethylamine (1.0 equivalent) according to the procedure of Example 5B to give the title compound.

4180

Example 5F4-((S)-2-Pyrrolidone-5-aminomethylcarbonyl)amino-2-phenylbenzoyl methionine

To a solution of the resultant compound from Example 5D (1.0 equivalent) in a 3:1 mixture of THF and water is added an excess of LiOH (1.5 equivalents). When hydrolysis is judged complete by TLC analysis, the solvent is evaporated and the remaining aqueous layer is acidified to pH = 3 and extracted into ethyl acetate which is dried and evaporated prior to purification by chromatography on silica gel.



Example 6

4-(2-pyridyloxy)-2-phenylbenzoylmethionine

Example 6A

4-Hydroxy-2-phenylbenzoic acid methyl ester

A solution of methyl 4-amino-2-phenylbenzoate (1.0 equivalent) in dilute aqueous H₂SO₄ is treated with NaNO₂ (1.1 equivalents) until an excess of nitrous acid persists to form the diazonium salt. This salt is then diluted further with water and heated. The mixture is extracted into ethyl acetate which is dried and evaporated. The title ester is purified by chromatography on silica gel.

Example 6B

4-(2-Pyridyloxy)-2-phenylbenzoic acid methyl ester

A solution of the resultant phenol from Example 6A (1.0 equivalent) is treated with 2-bromopyridine (1.0 equivalent) in the presence of a NaH (1.0 equivalent), or K₂CO₃ (2.0 equivalents) and copper (1.0 equivalent) in DMF or pyridine. The product is isolated by removal of the solvent and chromatography on silica gel.

Example 6C

4-(2-Pyridyloxy)-2-phenylbenzoic acid

A solution of the resultant ester from Example 6B (1.0 equivalent) in aqueous methanol is treated with NaOH (2.0 equivalents) and stirred until the reaction is deemed complete by TLC analysis. The mixture is acidified, diluted with water, and extracted into ethyl acetate which is dried and evaporated. Chromatography on silica gel provides the title product.

Example 6D

4-(2-Pyridyloxy)-2-phenylbenzoylmethionine methyl ester

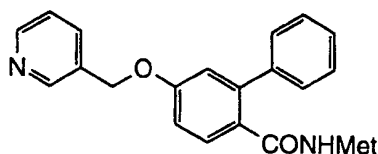
4220 The resultant product from Example 6C is coupled to methionine methyl ester according to the procedure of Example 1C to give the title compound.

Example 6E4-(2-Pyridyloxy)-2-phenylbenzoylmethionine methyl ester, alternate procedure

4225 A solution of 4-amino-2-phenylbenzoyl methionine methyl ester (1.0 equivalent) in dilute aqueous H₂SO₄ is treated with NaNO₂ (1.1 equivalents) until an excess of nitrous acid persists to form the diazonium salt. This salt is then diluted further with water and heated to form the phenol which is purified by chromatography on silica gel. A solution of this phenol (1.0 equivalent) is treated with 3-bromopyridine (1.0 equivalent) in the presence of a NaH (1.0 equivalent), or K₂CO₃ (2.0 equivalents) and copper (1.0 equivalent) in DMF or
4230 pyridine. The product is isolated by removal of the solvent and chromatography on silica gel.

Example 6F4-(2-pyridyloxy)-2-phenylbenzoylmethionine

4235 The resultant compound from Example 6E is hydrolyzed according to the procedure of Example 1B to give the title compound.

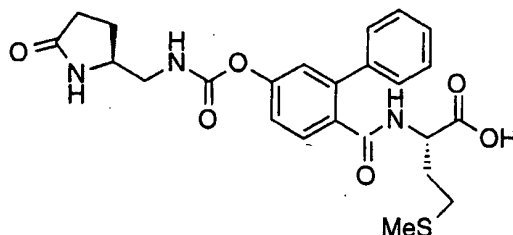


4240

Example 74-(3-pyridylmethylenoxy)-2-phenylbenzoylmethionine

The title compound is prepared as described in Example 6 with the exception that 2-bromopyridine is replaced by 3-chloromethylpyridine hydrochloride.

4245



Example 8

4250 4-((S)-2-Pyrrolidone-5-aminomethyl)carbonyloxy-2-phenylbenzoyl methionine

Example 8A

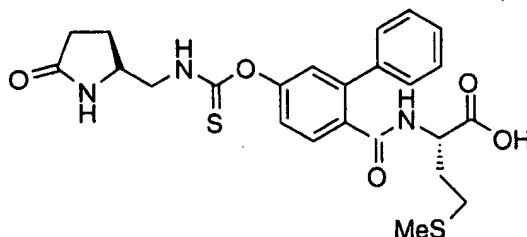
4-((S)-2-Pyrrolidone-5-aminomethyl)carbonyloxy-2-phenylbenzoyl methionine methyl ester

To a solution of 4-hydroxy-2-phenylbenzoyl methionine methyl ester (1.0 equivalent) from
4255 Example 6E in methylene chloride is added a solution of phosgene in toluene (1.0
equivalent) and *p*-dimethylaminopyridine (2.0 equivalents). When the reaction is judged
complete by TLC analysis, the solvent is evaporated with toluene chasers. The
chloroformate is reacted without further purification with (S)-5-aminomethyl-2-pyrrolidone
(1.0 equivalent) and triethylamine (1.0 equivalent) in dichloromethane. When judged
4260 complete by TLC analysis, the reaction is taken up in ethyl acetate and washed with 1N HCl
and brine, evaporated, and purified by chromatography on silica gel.

Example 8B

4-((S)-2-Pyrrolidone-5-aminomethyl)carbonyloxy-2-phenylbenzoyl methionine

4265 The resultant compound from Example 8A is hydrolyzed according to the procedure of
Example 1B to give the title product.

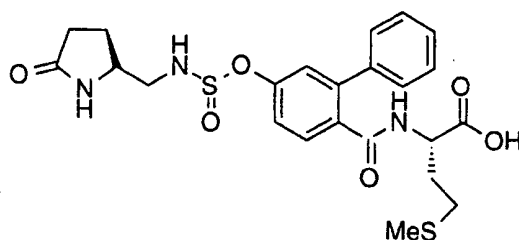


4270

Example 9

4-((S)-2-Pyrrolidone-5-aminomethyl)thiocarbonyloxy-2-phenylbenzoyl methionine methyl ester

The title compound is prepared as described in Example 8 with the exception that phosgene
4275 in toluene is replaced by thiophosgene.

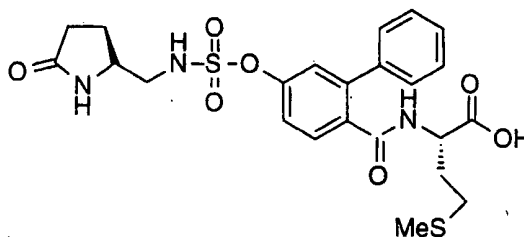


4280

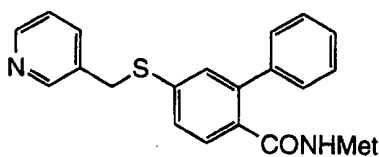
Example 104-((S)-2-Pyrrolidone-5-aminomethyl)sulfinyloxy)-2-phenylbenzoyl methionine

The title compound is prepared as described in Example 8 with the exception that phosgene in toluene is replaced by thionyl chloride.

4285

Example 114-((S)-2-Pyrrolidone-5-aminomethyl)sulfonyloxy)-2-phenylbenzoyl methionine

4290 The title compound is prepared as described in Example 8 with the exception that phosgene in toluene is replaced by sulfuryl chloride.



4295

Example 124-(3-Pyridylmethylthio)-2-phenylbenzoylmethionineExample 12A4-Mercapto-2-phenylbenzoic acid methyl ester

4300

A solution of methyl 4-amino-2-phenylbenzoic acid (1.0 equivalent) in dilute aqueous H_2SO_4 is treated with $NaNO_2$ (1.1 equivalents) to form the diazonium salt. The reaction is

4305 treated with S₈ (10 equivalents) and heated. The mixture is extracted into ethyl acetate which is dried and evaporated. The title thiophenol is purified by chromatography on silica gel.

Example 12B

4-(2-Pyridylmethylenethio)-2-phenylbenzoic acid methyl ester

4310 A solution of the resultant thiophenol (1.0 equivalent) from Example 12A is treated with 2-chloromethylpyridine hydrochloride (1.0 equivalent) in the presence of a NaH (2.0 equivalents), or K₂CO₃ (3.0 equivalent)s in DMF or pyridine. The product is isolated by removal of the solvent and chromatography on silica gel.

4315

Example 12C

4-(2-Pyridylthiomethylen)-2-phenylbenzoic acid

The resultant compound from Example 12B is hydrolyzed according to the procedure of Example 6C to give the title acid.

4320

Example 12D

4-(2-Pyridylthiomethylen)-2-phenylbenzoylmethionine methyl ester

The resultant product from Example 12C is coupled to methionine methyl ester according to the procedure of Example 1C to give the title compound.

4325

Example 12E

4-(2-Pyridylthiomethylen)-2-phenylbenzoylmethionine methyl ester, alternate procedure 1

4330 A solution of 4-amino-2-phenylbenzoyl methionine methyl ester (1.0 equivalent) in dilute aqueous H₂SO₄ is treated with NaNO₂ (1.1 equivalents) to form the diazonium salt. The reaction is treated with S₈ (10 equivalents) and heated. The mixture is extracted into ethyl acetate which is dried and evaporated to afford 2-phenyl-4-mercaptobenzoyl-methionine methyl ester. The thiophenol is purified by chromatography on silica gel. A solution of this
4335 thiophenol (1.0 equivalent) is treated with 2-chloromethylpyridine hydrochloride (1.0 equivalent) in the presence of a NaH (2.0 equivalents), or K₂CO₃ (3.0 equivalents) in DMF or pyridine. The product is isolated by removal of the solvent and chromatography on silica gel.

4340

Example 12F4-(2-Pyridylthiomethylen)-2-phenylbenzoylmethionine methyl ester, alternate procedure 2

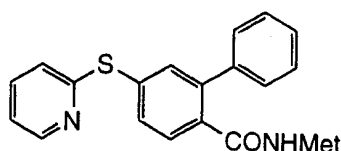
Methyl 4-amino-2-phenylbenzoate (100 mmol) is mixed in 50% sulfuric acid, and is cooled by a ice-water bath. To the above mixture with good stirring is added slowly a cold solution of sodium nitrite (110 mmol) in water, the reaction temperature is kept under 10 °C. Powdered anhydrous sodium carbonate (100 mmol) is carefully added to the cold reaction mixture in small portions, until the reaction mixture reaches pH 7 to 8. Then, the reaction mixture is added in small portions to a solution of sodium p-methoxybenzylsulfide (prepared from reaction 110 mmol of p-methoxybenzylthiol with 55 mmol of 2.0 M NaOH aqueous solution). After completion of the addition, the reaction mixture is refluxed until judged complete by TLC analysis. The reaction mixture is then extracted with ether, and the organic extracts are washed sequentially with aqueous sodium carbonate solution, water and brine, dried with anhydrous magnesium sulfate, filtered, and concentrated in vacuo. The residue is then purified by column chromatography on silica gel. The product thus obtained is dissolved in methanol and water, followed by addition of lithium hydroxide (200 mmol), and the mixture is refluxed until hydrolysis is judged complete by TLC analysis. The reaction mixture is then acidified with 6 N HCl, and extracted into ethyl acetate. The organic extracts are washed with brine, dried with anhydrous sodium sulfate, and concentrated in vacuo. The crude product obtained is redissolved in methylene chloride, followed by addition of 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide (1.1 equivalent) and 1-hydroxybenzotriazol (1.2 equivalent). The reaction is stirred until it is judged complete by TLC analysis, and then is diluted with ether. The mixture is washed with water, brine, dried over anhydrous magnesium sulfate, filtered, and concentrated in vacuo. The residue is then purified by column chromatography on silica gel. The resulting product is dissolved in trifluoroacetic acid and anisole (1.5 equivalent), and mercury diacetate (1.2 equivalent) is added. After TLC shows no starting material left, the reaction mixture is diluted with ether, washed with water, brine, dried over anhydrous magnesium sulfate, filtered, and concentrated in vacuo. The resulting crude material is purified by column chromatography to afford 2-phenyl-4-mercaptobenzoyl-methionine methyl ester. A solution of this thiophenol (1.0 equivalent) is treated with 2-chloromethylpyridine hydrochloride (1.0 equivalent) in the presence of a NaH (2.0 equivalents), or K₂CO₃ (3.0 equivalents) in DMF or pyridine. The product is isolated by removal of the solvent and chromatography on silica gel.

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Example 12G4-(3-Pyridylthiomethylen)-2-phenylbenzoylmethionine

The resultant compound from Example 12D is hydrolyzed according to the procedure of Example 1B to give the title product.

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Example 134-(2-Pyridylthio)-2-phenylbenzoylmethionine

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Example 13A4-Fluoro-2-phenyl benzoic acid methyl ester

4390 A solution of methyl 4-amino-2-phenylbenzoate (1.0 equivalent) in dilute aqueous HBF_4 is treated with NaNO_2 (1.1 equivalents) until an excess of nitrous acid persists. The mixture is extracted into ethyl acetate which is dried and evaporated. The title ester is purified by chromatography on silica gel.

Example 13B4-Fluoro-2-phenyl benzoic acid

4395 The resultant compound from Example 13A is hydrolyzed according to the procedure of Example 6C to give the title acid.

Example 13C4-Fluoro-2-phenyl benzoyl methionine methyl ester

4400 The resultant product from Example 13B is coupled to methionine methyl ester according to the procedure of Example 1C to give the title compound.

Example 13D4-(2-Pyridylthio)-2-phenyl benzoyl methionine methyl ester

4405 A mixture of the resultant fluorobenzoate from Example 13C (1.0 equivalent) and 2-mercaptopyridine (1.0 equivalent) is treated with K_2CO_3 (2.0 equivalents) or NaH (1.0 equivalent) in DMF or DMSO and is stirred until the reaction is judged complete by TLC analysis. The mixture is diluted with water and extracted into ethyl acetate which is dried and evaporated. Chromatography of the residue on silica gel affords the title compound.

4410

Example 13E4-(2-Pyridylthio)-2-phenyl benzoyl methionine methyl ester, alternate procedure 1

A solution of 4-amino-2-phenylbenzoyl methionine methyl ester (1.0 equivalent) in dilute aqueous H_2SO_4 is treated with NaNO_2 (1.1 equivalents) to form the diazonium salt. The

4415 reaction is treated with S₈ (10 equivalents) and heated. The mixture is extracted into ethyl acetate which is dried and evaporated. The title thiophenol is purified by chromatography on silica gel. A solution of this thiophenol (1.0 equivalent) is treated with 2-bromopyridine hydrobromide (1.0 equivalent) in the presence of a NaH (2.0 equivalent), or K₂CO₃ (3.0 equivalent)s in DMF or pyridine. The product is isolated by removal of the solvent and
4420 chromatography on silica gel.

Example 13F

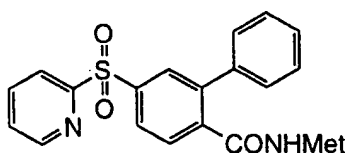
4-(2-Pyridylthio)-2-phenyl benzoyl methionine methyl ester, alternate procedure 2

A solution of the resultant thiophenol from Example 12A (1.0 equivalent) is treated with 2-bromopyridine hydrobromide (1.0 equivalent) in the presence of a NaH (2.0 equivalents),
4425 or K₂CO₃ (3.0 equivalents) in DMF or pyridine. The product is isolated by removal of the solvent and chromatography on silica gel. The resultant ester is hydrolyzed according to the procedure of Example 6C and then is coupled to methionine methyl ester according to the procedure of Example 1C to give the title compound.

Example 13G

4-(2-Pyridylthio)-2-phenylbenzoylmethionine

The resultant compound from Example 13D is hydrolyzed according to the procedure of Example 1B to give the title product.



Example 14

4-(2-Pyridylsulfonyl)-2-phenylbenzoylmethionine

Example 14A

4-(2-Pyridylsulfonyl)-2-phenylbenzoic acid methyl ester

A solution of 4-(2-pyridylthio)-2-phenylbenzoic acid methyl ester (Example 13F) is
4445 carefully treated with two equivalents of *meta*-chloroperbenzoic acid in methylene chloride at low temperature and the reaction is then quenched with aqueous Na₂SO₃ when judged complete by TLC analysis. The layers are separated and the organic phase is extracted with

aqueous NaHCO₃ to remove the *m*-chlorobenzoic acid. The product is isolated by removal of the solvent and is purified by chromatography on silica gel.

Example 14B

4-(2-Pyridylsulfonyl)-2-phenylbenzoic acid

The resultant compound from Example 14A is hydrolyzed according to the procedure of Example 6C to give the title acid.

Example 14C

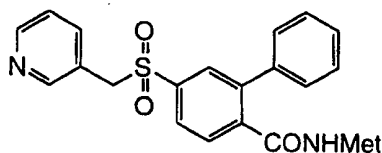
4-(2-pyridylsulfonyl)-2-phenylbenzoylmethionine methyl ester

The resultant product from Example 14B is coupled to methionine methyl ester according to the procedure of Example 1C to give the title compound.

Example 14D

4-(2-Pyridylsulfonyl)-2-phenylbenzoylmethionine

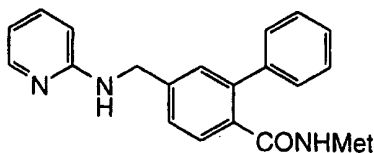
The resultant compound from Example 14C is hydrolyzed according to the procedure of Example 1B to give the title product.



Example 15

4-(3-Pyridylthiomethylene)-2-phenylbenzoylmethionine

The title compound is prepared from the resultant product of Example 12B using the procedures from Example 14.



Example 16

4-[(2-Aminopyridyl)methylene]-2-phenylbenzoylmethionine

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Example 16A2-Phenylterephthalic acid mono methyl ester

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A solution of 4-bromo-2-phenylbenzoic acid methyl ester (1.0 equivalent), Pd(OAc)₂ (0.05 equivalent) and DPPE (1.0 equivalent) is heated in DMF to 65° C under 4 atm. of carbon monoxide until TLC analysis indicates that the reaction is complete. The reaction mixture is poured into water and extracted with ethyl acetate which is dried and evaporated. The product is purified by chromatography on silica gel.

Example 16B4-(Hydroxymethyl)-2-phenylbenzoic acid methyl ester

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The resultant acid from Example 16A (1.0 equivalent) is treated with a slight excess of N-methylmorpholine (1.1 equivalent) and isobutylchloroformate (1.0 equivalent) in THF at 0° C. The mixture is then treated with NaBH₄ (1.0 equivalent) and aqueous NaHCO₃ and stirred at 0° C until the reaction is judged complete by TLC analysis. The mixture is poured into dilute aqueous acid and extracted into ethyl acetate which is dried and evaporated. The product is purified by chromatography on silica gel.

Example 16C4-(Hydroxymethyl)-2-phenylbenzoic acid

4500

The resultant compound from Example 16B is hydrolyzed according to the procedure of Example 6C to give the title acid.

Example 16D4-(Hydroxymethyl)-2-phenylbenzoyl methionine methyl ester

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The resultant product from Example 16C is coupled to methionine methyl ester according to the procedure of Example 1C to give the title compound.

Example 16E4-formyl-2-phenylbenzoyl methionine methyl ester

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A mixture of the resultant alcohol from Example 16D (1.0 equivalent), N-methylmorpholine-N-oxide (1.5 equivalents), molecular sieves, and a catalytic amount of TPAP is stirred in a CH₂Cl₂/acetonitrile mixture until the reaction is judged complete by TLC analysis. The mixture is diluted with ethyl ether and filtered through SiO₂. The product is purified by chromatography on silica gel.

Example 16F4-(formyl)-2-phenylbenzoyl methionine methyl ester, alternate procedure

A mixture of (2-phenyl-4-bromobenzoyl) methionine methyl ester (100 mmol), 4,4,6-trimethyl-2-vinyl-1,3,2-dioxaborinane (100 mmol), tetrakis(triphenylphosphine)palladium (0) (3 mmol) in toluene and 2 M sodium carbonate in water (100 mL) is heated at 80 °C until the starting methyl ester disappears. The resulting mixture is extracted with ether, and washed with water, brine, dried over anhydrous magnesium sulfate, filtered, and concentrated in vacuo. The residue is then purified by column chromatography on silica gel. To a solution of the resulting vinyl compound in dioxane/water (4/1) is added osmium tetroxide (0.03 equivalent), N-methylmorpholine N-oxide (3 equivalents), and the reaction is stirred at 25 °C until TLC analysis shows the reaction to be complete. The reaction mixture is extracted with ether, which is washed with water and brine, dried over anhydrous magnesium sulfate, filtered, and concentrated in vacuo. The residue is then purified by column chromatography on silica gel to afford the title product.

Example 16G4-(Hydroxymethyl)-2-phenylbenzoyl methionine methyl ester, alternate procedure

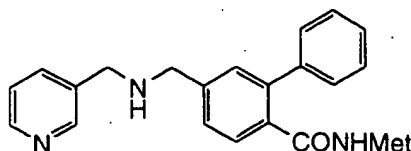
To a solution of the resultant compound from Example 16E in ethanol at 0 °C is added sodium borohydride (0.5 equivalent), and the reaction is stirred at 0 °C until TLC analysis shows the reaction to be complete. The reaction mixture is extracted with ether, which is washed with water and brine, dried over anhydrous magnesium sulfate, filtered, and concentrated in vacuo. The residue is then purified by column chromatography on silica gel to afford the title product.

Example 16H4-[(2-Aminopyridyl)methylene]-2-phenylbenzoylmethionine methyl ester

A mixture of the resultant aldehyde from Example 16E (1.0 equivalent), 2-aminopyridine (1.0 equivalent) and NaCNBH₃ (1.5 equivalents) in methanol/acetic acid is stirred until the reaction is judged complete by TLC analysis. The mixture is poured into aqueous NaHCO₃ and extracted into ethyl acetate which is dried and evaporated. Chromatography of the residue on silica gel affords the title compound.

Example 16I4-[(2-Aminopyridyl)methylene]-2-phenylbenzoylmethionine

The resultant compound from Example 16H is hydrolyzed according to the procedure of
 4555 Example 1B to give the title product.

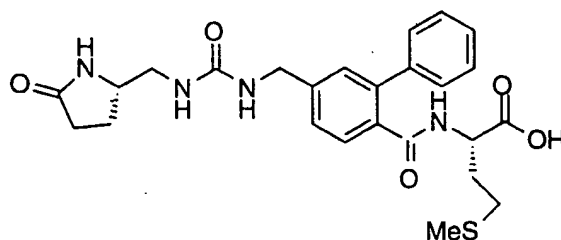


4560

Example 174-[(3-aminomethyl)pyridyl]methylene]-2-phenylbenzoyl methionine

Using the procedures of Examples 16F-G and replacing 2-aminopyridine with 3-aminomethylpyridine affords the title product.

4565

Example 184-((S)-2-Pyrrolidone-5-aminomethylcarbonyl)aminomethyl-2-phenylbenzoyl methionine

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Example 18A4-(Azidomethyl)-2-phenylbenzoyl methionine methyl ester

To triphenylphosphine (1.0 equivalent) in tetrahydrofuran (THF) at -78° C is added diethyl azodicarboxylate (1.0 equivalent) in THF. To this mixture is added a solution of hydrazoic acid in benzene (2.0 equivalents) and then the resultant compound from Example 16D (1.0 equivalent). After one hour the mixture was warmed to room temperature, stirred until the
 4575 reaction is judged complete by TLC analysis, evaporated and chromatographed on silica gel to afford the title product.

4580

Example 18B4-(Aminomethyl)-2-phenylbenzoyl methionine methyl ester

To the resultant compound from Example 18A in methanol is added triethylamine (3.0 equivalent) and propane 1,3-dithiol (3.0 equivalents). After the reaction is judged complete

by TLC analysis, the mixture is filtered and evaporated. Chromatography of the residue on
 4585 silica gel provides the title product.

Example 18C

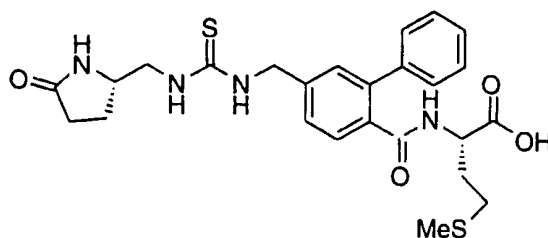
4-((S)-2-Pyrrolidone-5-aminomethylcarbonyl)aminomethyl-2-phenylbenzoyl methionine methyl ester

4590 To a solution of the resultant compound from Example 18B (1.0 equivalent) in methylene chloride is added triphosgene (0.33 equivalent) and triethyl amine (2.0 equivalents). This intermediate is reacted without further purification with (S)-5-aminomethyl-2-pyrrolidone (1.0 equivalent) and triethylamine (1.0 equivalent). When judged complete by TLC
 4595 analysis, the reaction is taken up in ethyl acetate and washed with 1N HCl and brine, evaporated, and purified by chromatography on silica gel.

Example 18D

4-((S)-2-Pyrrolidone-5-aminomethylcarbonyl)aminomethyl-2-phenylbenzoyl methionine

The resultant compound from Example 18C is hydrolyzed according to the procedure of
 4600 Example 1B to give the title product.



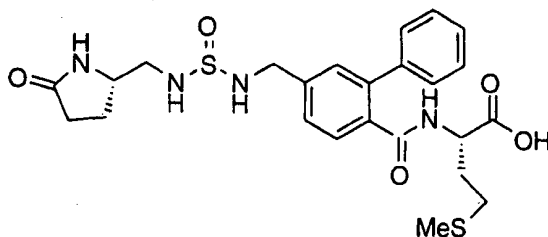
4605

Example 19

4-((S)-2-Pyrrolidone-5-aminomethylthiocarbonyl)aminomethyl-2-phenylbenzoyl methionine

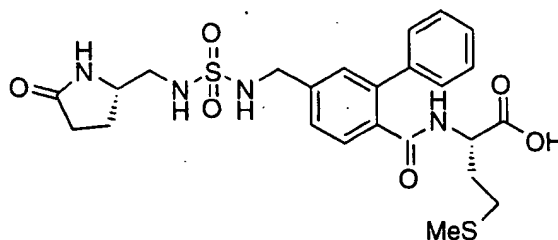
The title compound is prepared as described in Example 18 with the exception that triphosgene (0.33 equivalent) is replaced by thiophosgene (1.0 equivalent).

4610



Example 204-((S)-2-Pyrrolidone-5-aminomethylsulfinyl)aminomethyl-2-phenylbenzoyl methionine

4615 The title compound is prepared as described in Example 18 with the exception that triphosgene (0.33 equivalent) is replaced by thionyl chloride (1.0 equivalent).

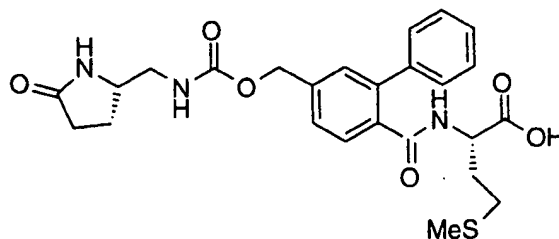


4620

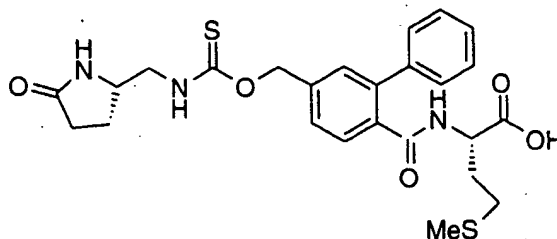
Example 214-((S)-2-Pyrrolidone-5-aminomethylsulfonyl)aminomethyl-2-phenylbenzoyl methionine

Using the Procedure of Example 4 with the resultant compound from Example 18B affords the title product.

4625

Example 224-((S)-2-Pyrrolidone-5-aminomethyl)carbonyloxymethylene)-2-phenylbenzoyl methionine

4630 Using the procedure of Example 8 with the resultant compound from Example 16D provides the title product.

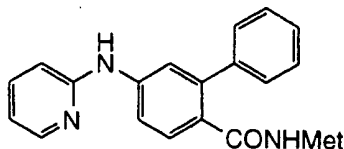


4635

Example 23

4-((S)-2-Pyrrolidone-5-aminomethyl)thiocarbonyloxymethylene)-2-phenylbenzoyl
methionine

Using the procedure of Example 8 with the resultant compound from Example 16D and replacing triphosgene (0.33 equivalent) with thiophosgene (1.0 equivalent) provides the title product.



Example 24

4-(2-Aminopyridyl)-2-phenylbenzoylmethionine

Example 24A

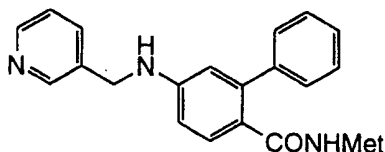
4-(2-Aminopyridyl)-2-phenylbenzoylmethionine methyl ester

4-Amino-2-phenylbenzoyl methionine (1.0 equivalent) methyl ester and 2-bromopyridine hydrobromide (1.0 equivalent) in pyridine are heated until the reaction is judged complete by TLC analysis. The solvent is evaporated and the residue is taken up in ethyl acetate which is washed with water and brine, dried, and evaporated. Chromatography on silica gel affords the title product.

Example 24B

4-(2-Aminopyridyl)-2-phenylbenzoylmethionine

The resultant compound from Example 24A is hydrolyzed according to the procedure of Example 1B to give the title product.



Example 25

4-(3-Aminomethylpyridyl)-2-phenylbenzoylmethionine

Example 25A

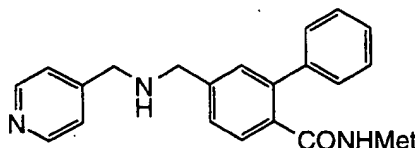
4-(3-Aminomethylpyridyl)-2-phenylbenzoylmethionine methyl ester

A mixture of 3-pyridinecarboxaldehyde (1.0 equivalent), 4-amino-2-phenylbenzoyl methionine methyl ester (1.0 equivalent) and NaCNBH₃ (1.0 equivalent) in methanol/acetic acid is stirred until the reaction is judged complete by TLC analysis. The mixture is poured into aqueous NaHCO₃ and extracted into ethyl acetate which is dried and evaporated. Chromatography of the residue on silica gel affords the title compound.

Example 25B

4-(3-Aminomethylpyridyl)-2-phenylbenzoylmethionine

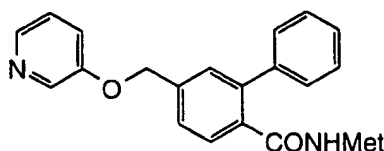
The resultant compound from Example 25A is hydrolyzed according to the procedure of Example 1B to give the title product.



Example 26

4-[(4-aminomethylpyridyl)methylene]-2-phenylbenzoylmethionine

Using the procedures of Examples 25 with the resultant amine from Example 18B and 3-pyridinecarboxaldehyde affords the title product.



Example 27

4-(3-Pyridyloxymethylene)-2-phenylbenzoylmethionine

Example 27A

4-(p-Toluenesulfonyloxy)-2-phenylbenzoylmethionine methyl ester

The resultant compound from Example 16D (1.0 equivalent) and *p*-toluenesulfonyl chloride (1.0 equivalent) in pyridine are stirred until the reaction is judged complete by TLC analysis. The solvent is evaporated and the residue is taken up in ethyl acetate which is washed with water and brine, dried, and evaporated. Chromatography on silica gel affords the title product.

Example 27B

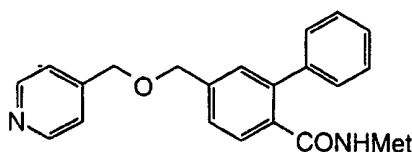
4-(3-Pyridyloxymethylene)-2-phenylbenzoylmethionine methyl ester

3-Hydroxypyridine (1.0 equivalent) is treated with sodium hydride (1.0 equivalent) in DMSO, then the resultant compound from Example 27A (1.0 equivalent) is added. When judged complete by TLC analysis, the reaction is diluted with water and ethyl acetate, the organic layer is dried and concentrated, and the crude title compound is purified by chromatography on silica gel.

Example 27C

4-(3-Pyridyloxymethylene)-2-phenylbenzoylmethionine

The resultant compound from Example 27B is hydrolyzed according to the procedure of Example 1B to give the title product.



Example 28

4-(3-Pyridylmethoxymethylene)-2-phenylbenzoylmethionine

Example 28A

4-(3-Pyridylmethoxymethylene)-2-phenylbenzoylmethionine methyl ester

Using the procedure of Example 27B but replacing 3-hydroxypyridine with 3-hydroxymethylpyridine affords the title compound.

Example 28B

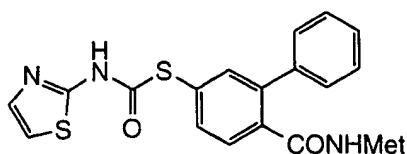
4-(3-Pyridylmethoxymethylene)-2-phenylbenzoylmethionine methyl ester, alternate procedure

The resultant compound from Example 16D (1.0 equivalent) is treated with sodium hydride (2.0 equivalents) in DMSO, then 3-chloromethylpyridine hydrochloride (1.0 equivalent) is added. When judged complete by TLC analysis, the reaction is diluted with water and ethyl acetate, the organic layer is dried and concentrated, and the crude title compound is purified by chromatography on silica gel.

Example 28C

4-(3-Pyridylmethoxymethylene)-2-phenylbenzoylmethionine methyl ester

The resultant compound from Example 28A is hydrolyzed according to the procedure of Example 1B to give the title product.

Example 29{2-Phenyl-4-[(thiazol-2-ylamino)carbonylthio]benzoyl}-methionineExample 29AThiazol-2-ylisocyanate

A solution of 2-aminothiazol (1.0 mmol), triphosgene (0.34 mmol) and triethylamine (1.0 mmol) in toluene (10 mL) is refluxed until TLC shows no starting amine left. The solvent is then removed in vacuo, and the resulting material is used without further purification.

Example 29B{2-Phenyl-4-[(thiazol-2-ylamino)carbonylthio]benzoyl}-methionine methyl ester

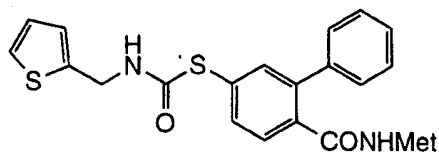
A solution of 2-phenyl-4-mercaptobenzoyl-methionine methyl ester from example 12E or 12F (1.0 mmol) and the isocyanate prepared in example 29A (1.0 mmol) in THF is refluxed until TLC shows no thiol left. The solvent is then evaporated in vacuo, and the residue is purified by column chromatography on silica gel to give the title compound.

Example 29C{2-Phenyl-4-[(thiazol-2-ylamino)carbonylthio]benzoyl}-methionine methyl ester, alternate procedure

To a solution of 2-phenyl-4-mercaptobenzoyl-methionine methyl ester from example 12E or 12F (1 equivalent) in methylene chloride is added a solution of phosgene in toluene (1.0 equivalent) and *p*-dimethylaminopyridine (2.0 equivalents). When the reaction is judged complete by TLC analysis, the solvent is evaporated with toluene chasers. The thiochloroformate is reacted without further purification with 2-aminothiazol (1.0 equivalent) and triethylamine (1.0 equivalent) in dichloromethane. When judged complete by TLC analysis, the reaction is taken up in ethyl acetate and washed with 1N HCl and brine, evaporated, and purified by chromatography on silica gel.

Example 29D{2-Phenyl-4-[(thiazol-2-ylamino)carbonylthio]benzoyl}-methionine

The resultant compound from Example 29B is hydrolyzed according to the procedure of
 4770 Example 1B to give the title product.

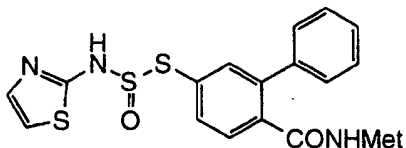


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Example 30{2-Phenyl-4-[(thien-2-ylmethylamino)carbonylthio]benzoyl}-methionine

Using the procedure of Example 29 but replacing 2-aminothiazol with thien-2-ylmethylamine affords the title product.

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Example 31{2-Phenyl-4-[(thiazol-2-ylamino)thionylthio]benzoyl}-methionine

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Example 31A(N-Thionyl)thiazol-2-ylamine

A solution of 2-aminothiazol (1.0 mmol), in thionyl chloride is heated at reflux until the reaction is judged to be complete by TLC analysis. Then, the excess thionylchloride is distilled out in vacuo. The resulting material is used without further purification.

4790

Example 31B{2-Phenyl-4-[(thiazol-2-ylamino)thionylthio]benzoyl}-methionine methyl ester

Using the procedure of Example 29B but replacing the resultant product from Example 29A with the resultant product from Example 31A affords the title compound.

4795

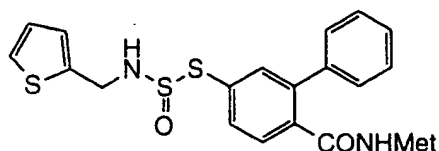
Example 31C{2-Phenyl-4-[(thiazol-2-ylamino)thionylthio]benzoyl}-methionine methyl ester, alternate procedure

Using the procedure of Example 29C but replacing phosgene in toluene with thionyl
 4800 chloride affords the title compound.

Example 31D

{2-Phenyl-4-[(thiazol-2-ylamino)thionylthio]benzoyl}-methionine

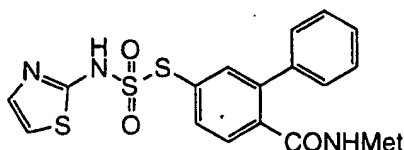
The resultant compound from Example 31B is hydrolyzed according to the procedure of
 4805 Example 1B to give the title product.



Example 32

{2-Phenyl-4-[(thien-2-ylmethylamino)thionylthio]benzoyl}-methionine

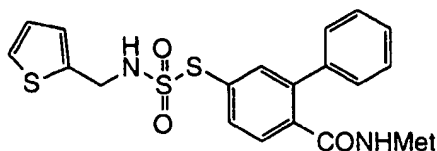
Using the procedure of Example 31 but replacing 2-aminothiazol with thien-2-
 ylmethylamine affords the title product.



Example 33

{2-Phenyl-4-[(thiazol-2-ylamino)sulfonylthio]benzoyl}-methionine methyl ester

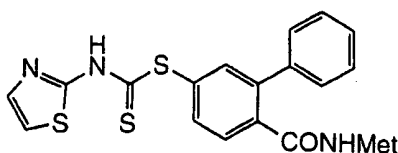
Using the procedure of Example 31 but replacing thionyl chloride with sulfonyl chloride
 4820 affords the title product.



Example 34

{2-Phenyl-4-[(thien-2-ylmethylamino)sulfonylthio]benzoyl}-methionine

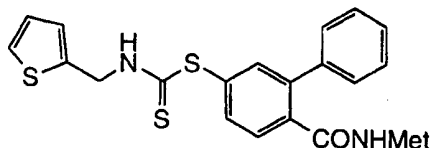
Using the procedure of Example 31 but replacing 2-aminothiazol with thien-2-
 4825 ylmethylamine and replacing thionyl chloride with sulfonyl chloride affords the title product.



4830

Example 35[2-Phenyl-4-[(thiazol-2-ylamino)thiocarbonylthio]benzoyl]-methionine

Using the procedure of Example 29 and replacing triphosgene (0.34 mmol) or a solution of phosgene in toluene (1.0 equivalent) with thiophosgene (1.0 mmol) affords the title product.

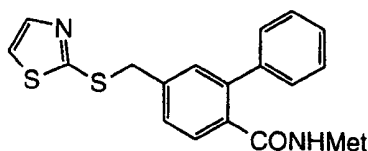


4835

Example 36[2-Phenyl-4-[(thien-2-ylmethylamino)thiocarbonylthio]benzoyl]-methionine

Using the procedure of Example 29 and replacing triphosgene (0.34 mmol) or a solution of phosgene in toluene (1.0 equivalent) with thiophosgene (1.0 mmol) and replacing 2-aminothiazol with thien-2-ylmethylamine affords the title product.

4840



4845

Example 37[2-Phenyl-4-[(thiazol-2-yl)thiomethyl]benzoyl]-methionineExample 37A[2-Phenyl-4-[thiomethyl]benzoyl]-methionine methyl ester

The resultant product from Example 27A is dissolved DMF/water (2/1), and sodium hydrosulfide (5 equivalent) is added to the reaction mixture. The reaction is stirred until TLC analysis shows that the reaction is complete. Then, the reaction mixture is acidified with 3 N HCl to about pH 4, extracted with ether, and washed with water and brine, dried over anhydrous magnesium sulfate, filtered, and concentrated in vacuo. The residue is purified with column chromatography on silica gel to give the title compound.

4855

Example 37B[2-Phenyl-4-[thiomethyl]benzoyl]-methionine methyl ester, alternate procedure

To triphenylphosphine (1.2 equivalents) in THF at -78 °C is added diethylazodicarboxylate (1.2 equivalents) in THF. After 10 min thiolacetic acid (1.3 equivalents) in THF is added followed by the resultant compound from Example 16D (1. equivalent) in THF. The reaction is stirred at -78 °C for 1 h and then at ambient temperature until it is judged to be complete by TLC analysis. The mixture is evaporated and the residue is taken up in methanol and is treated with K₂CO₃ (2 equivalents). When the reaction is judged to be complete by TLC analysis, the solvent is evaporated and the residue is chromatographed on silica gel to afford the title product.

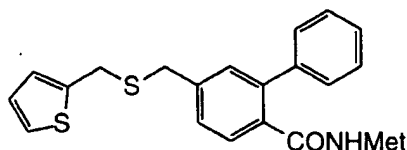
Example 37C

{2-Phenyl-4-[(thiazol-2-yl)thiomethyl]benzoyl}-methionine methyl ester

A mixture of the resultant thiol from Example 37A (1 mmol), 2-bromothiazole (1.5 mmol), and anhydrous potassium carbonate (5 mmol) in DMF is stirred at 100 °C until TLC analysis shows that the starting thiol disappeared. Then, the reaction mixture is diluted with water, extracted with ether, and washed with water and brine, dried over anhydrous magnesium sulfate, filtered, and concentrated in vacuo. The residue is purified by column chromatography on silica gel to give the title compound.

{2-Phenyl-4-[(thiazol-2-yl)thiomethyl]benzoyl}-methionine

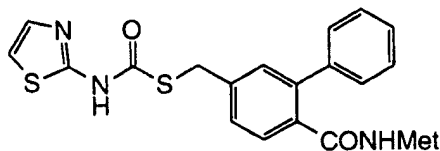
The resultant compound from Example 37C is hydrolyzed according to the procedure of Example 1B to give the title product.



Example 38

{2-Phenyl-4-[(thien-2-yl)methyl]thiomethyl]benzoyl}-methionine

Using the procedure of Example 37 and replacing 2-bromothiazole with 2-bromomethylthiophene affords the title product.

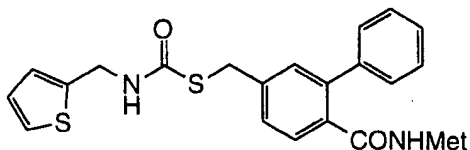


Example 39

4890

{2-Phenyl-4-[(thiazol-2-ylamino)carbonylthiomethyl]benzoyl}-methionine

Using the procedure of Example 29 with the resultant product from Example 37A affords the title product.

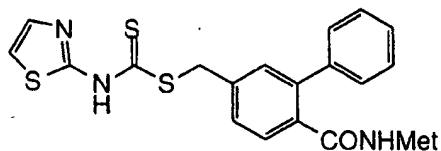


4895

Example 40{2-Phenyl-4-[(thiazol-2-ylamino)carbonylthiomethyl]benzoyl}-methionine

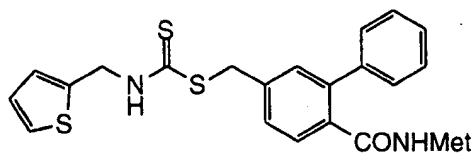
Using the procedure of Example 29 with the resultant product from Example 37A and replacing 2-aminothiazol with thien-2-ylmethylamine affords the title product.

4900

Example 41{2-Phenyl-4-[(thiazol-2-ylamino)thiocarbonylthiomethyl]benzoyl}-methionine

4905

Using the procedure of Example 29 with the resultant product from Example 37A and replacing triphosgene (0.34 mmol) or a solution of phosgene in toluene (1.0 equivalent) with thiophosgene (1.0 mmol) affords the title product.

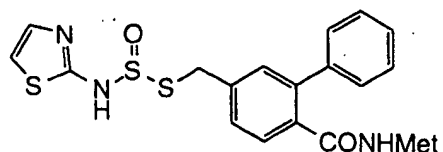


4910

Example 42{2-Phenyl-4-[(thiazol-2-ylamino)thiocarbonylthiomethyl]benzoyl}-methionine

Using the procedure of Example 29 with the resultant product from Example 37A, replacing triphosgene (0.34 mmol) or a solution of phosgene in toluene (1.0 equivalent) with thiophosgene (1.0 mmol), and replacing 2-aminothiazol with thien-2-ylmethylamine affords the title product.

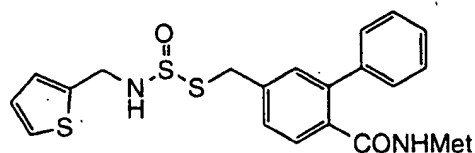
4915



Example 43

[2-Phenyl-4-[(thiazol-2-ylamino)thionylthiomethyl]benzoyl]-methionine

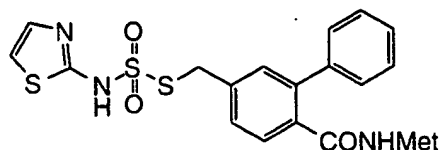
Using the procedure of Example 31 with the resultant product from Example 37A affords the title product.



Example 44

[2-Phenyl-4-[(thien-2-ylmethylamino)thionylthiomethyl]benzoyl]-methionine

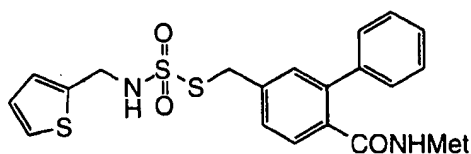
Using the procedure of Example 31 with the resultant product from Example 37A and replacing 2-aminothiazol with thien-2-ylmethylamine affords the title product.



Example 45

[2-Phenyl-4-[(thiazol-2-ylamino)sulfonylthiomethyl]benzoyl]-methionine

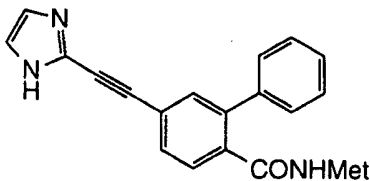
Using the procedure of Example 31 with the resultant product from Example 37A and replacing thionyl chloride with sulfonyl chloride affords the title product.



Example 46

[2-Phenyl-4-[(thien-2-ylmethylamino)sulfonylthiomethyl]benzoyl]-methionine

Using the procedure of Example 31 with the resultant product from Example 37A, replacing
 4945 thionyl chloride with sulfuryl chloride, and replacing 2-aminothiazol with thien-2-
 ylmethylamine affords the title product.



4950 Example 47

{4-[2-(Imidazol-2-yl)ethynyl]-2-phenylbenzoyl}methionine

Example 47A

(4-Ethynyl-2-phenylbenzoyl)methionine methyl ester

4955 A mixture of (2-phenyl-4-bromobenzoyl)-methionine methyl ester (100 mmol),
 diethylamine (300 mmol), trimethylsilylacetylene (110 mmol), bis(triphenylphosphine)
 palladium diacetate (5 mmol) and copper(I) iodide (3 mmol) in toluene is heated at 60 °C
 until TLC analysis indicates the starting methyl ester has disappeared. The reaction mixture
 is concentrated in vacuo, redissolved in ether, filtered through silica gel, and concentrated.

4960 The residue is then dissolved in THF, and is treated with tetrabutylammonium fluoride (120
 mmol). After TLC analysis indicates that no starting material is left, the reaction mixture is
 diluted with ether, washed with water and brine, dried over anhydrous magnesium sulfate,
 filtered, and concentrated in vacuo. The residue is then purified with column
 chromatography on silica gel to give the title product.

4965 Example 47B

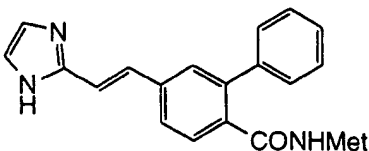
{4-[2-(Imidazol-2-yl)ethynyl]-2-phenylbenzoyl}-methionine methyl ester

The resultant product from Example 47A (5 mmol) is mixed with 4-bromoimidazole (5
 mmol), diethylamine (1 mL), bis(triphenylphosphine) palladium diacetate (0.1 mmol) and
 4970 copper(I) iodide (0.1 mmol) in toluene. The mixture is stirred at 25 °C until TLC analysis
 indicates the reaction is complete. The reaction mixture is concentrated in vacuo, and the
 residue is purified with column chromatography on silica gel to give the title product.

Example 47C

4975 {4-[2-(Imidazol-2-yl)ethynyl]-2-phenylbenzoyl}-methionine

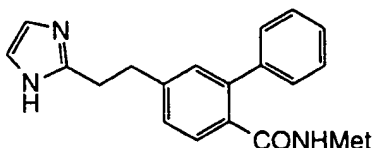
The resultant compound from Example 47B is hydrolyzed according to the
 procedure of Example 1B to give the title product.



Example 48

{4-[2-(Imidazol-4-yl)ethenyl]-2-phenylbenzoyl}-methionine

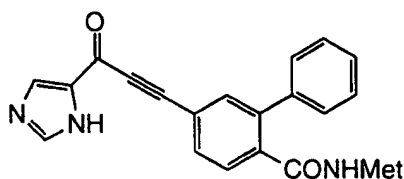
The resultant acetylene (3 mmol) from Example 47 is mixed with Lindlar catalyst (50 mg), 5 drops of quinoline in ethyl acetate. The reaction mixture is attached to a hydrogenation apparatus, and then is detached from the apparatus after about 95% of the theoretical hydrogen has been absorbed. The reaction mixture is filtered and concentrated in vacuo. The crude product is purified with a column chromatography on silica gel to give the title compound.



Example 49

{4-[2-(Imidazol-4-yl)ethyl]-2-phenylbenzoyl}-methionine

The resultant olefin (1 mmol) from Example 48 is mixed with 5% palladium on carbon (100 mg) in ethyl acetate. The reaction mixture is attached to a hydrogenation apparatus, and then is detached from the apparatus after about 95% of the theoretical hydrogen has been absorbed. The reaction mixture is filtered and concentrated in vacuo. The crude product is purified with a column chromatography on silica gel to give the title compound.



Example 50

{4-[2-(Imidazol-4-yl)carbonyl]ethynyl]-2-phenylbenzoyl}-methionine

Example 50A

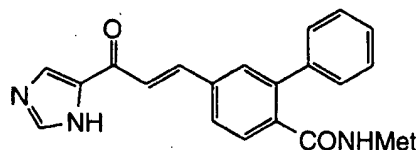
{4-[2-(Imidazol-4-yl)carbonyl]ethynyl]-2-phenylbenzoyl}-methionine methyl ester

A stainless autoclave containing the resultant product from Example 47A (5 mmol), 4-bromoimidazole (5 mmol), 1,1'-bis(diphenylphosphine)-ferrocenepalladium dichloride (0.1 mmol), and triethylamine (10 mL) is flushed with nitrogen, and pressurized to 20 atm with carbon monoxide. The reaction mixture is stirred at 120 °C until judged complete by TLC analysis. After cooling, the triethylamine is evaporated in vacuo, and the residue is purified by column chromatography on silica gel to give the title compound.

Example 50B

{4-[2-(Imidazol-4-ylcarbonyl)ethynyl]-2-phenylbenzoyl}-methionine

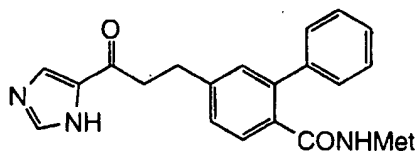
The resultant compound from Example 50A is hydrolyzed according to the procedure of Example 1B to give the title product.



Example 51

{4-[2-(Imidazol-4-ylcarbonyl)ethenyl]-2-phenylbenzoyl}-methionine

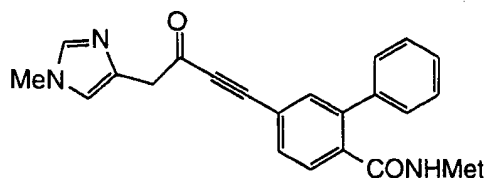
Using the procedure of Example 48 with the resultant compound from Example 50 affords the title product.



Example 52

{4-[2-(Imidazol-4-ylcarbonyl)ethyl]-2-phenylbenzoyl}-methionine

Using the procedure of Example 49 with the resultant compound from Example 51 affords the title product.



Example 53

5035 {4-[4-(1-Methylimidazol-4-yl)-3-keto-1-butynyl]-2-phenylbenzoyl}-methionine

Example 53A

{4-[4-(1-Methylimidazol-4-yl)-3-keto-1-butynyl]-2-phenylbenzoyl}-methionine methyl ester

5040 To a solution of 1-methyl-4-imidazoleacetic acid (5 mmol) in methylene chloride at 0 °C is added oxalyl chloride (6 mmol) and DMF (0.05 mmol). After 30 minute, the solvent is evaporated in vacuo. The residue is redissolved in dichloromethane, followed by the addition of the resultant acetylene from Example 47A (5 mmol), triethylamine (10 mmol), and copper(I) iodide (1 mmol). The reaction is stirred at 25 °C until TLC analysis indicates

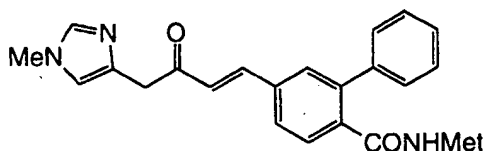
5045 no starting material is left in the reaction mixture. The reaction is diluted with ether, washed with water and brine, dried over anhydrous magnesium sulfate, filtered, and concentrated in vacuo. The residue is then purified by column chromatography on silica gel to give the title compound.

5050 Example 53B

{4-[4-(1-Methylimidazol-4-yl)-3-keto-1-butynyl]-2-phenylbenzoyl}-methionine

The resultant compound from Example 53A is hydrolyzed according to the procedure of Example 1B to give the title product.

5055

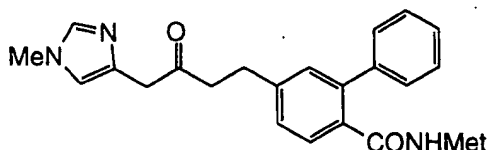


Example 54

{4-[4-(1-Methylimidazol-4-yl)-3-keto-1-butenyl]-2-phenylbenzoyl}-methionine

Using the procedure of Example 48 with the resultant compound from Example 53 affords

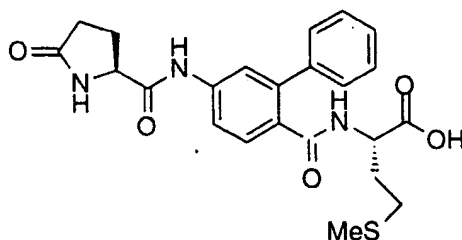
5060 the title product.



Example 55

5065 {4-[4-(1-Methylimidazol-4-yl)-3-keto-1-butenyl]-2-phenylbenzoyl}-methionine

Using the procedure of Example 49 with the resultant compound from Example 53 affords the title product.



5070

Example 56(S) Pyroglutamyl-(4-amino-2-phenyl)benzoyl methionineExample 56A

5075

(S) Pyroglutamyl-(4-amino-2-phenyl)benzoyl methionine methyl ester

To a solution of 4-amino-2-phenylbenzoyl methionine methyl ester (1.0 equivalent) in dimethylformamide (DMF) is added 3-hydroxy-1,2,3-benzotriazin-4(3H)-one (1.5 equivalents) followed by pyroglutamic acid (1.0 equivalent) and 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (1.5 equivalents). When judged complete by TLC analysis, the reaction is taken up in ethyl acetate which is washed with 1N HCl and saturated brine, and then is dried and evaporated. The crude reaction mixture is purified by column chromatography to afford the title product.

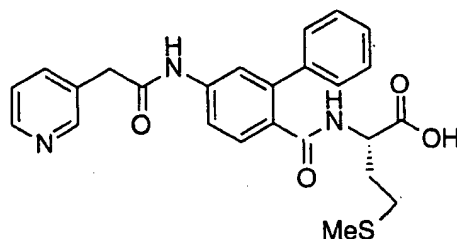
5080

Example 56B

5085

(S) Pyroglutamyl-(4-amino-2-phenyl)benzoyl methionine

The resultant compound from Example 56A is hydrolyzed according to the procedure of Example 1B to give the title product.

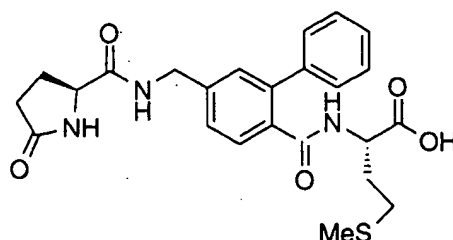


5090

Example 57(S) Pyroglutamyl-(4-amino-2-phenyl)benzoyl methionine

Using the procedure of Example 56 and replacing pyroglutamic acid with 3-pyridylacetic acid affords the title product.

5095

Example 58

(S) Pyroglutamyl-(4-aminomethyl-2-phenyl)benzoyl methionine

5100

Example 58A

(S) Pyroglutamyl-(4-aminomethyl-2-phenyl)benzoyl methionine methyl ester

To a solution of the resultant amine from Example 18B (1.0 equivalent) in dimethylformamide (DMF) is added 3-hydroxy-1,2,3-benzotriazin-4(3H)-one (1.5 equivalents) followed by pyroglutamic acid (1.0 equivalent) and 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (1.5 equivalents). When judged complete by TLC analysis, the reaction is taken up in ethyl acetate which is washed with 1N HCl and saturated brine, and then is dried and evaporated. The crude reaction mixture is purified by column chromatography to afford the title product.

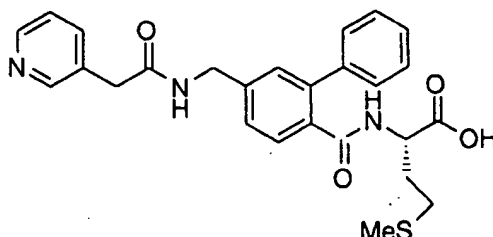
5110

Example 58B

(S) Pyroglutamyl-(4-aminomethyl-2-phenyl)benzoyl methionine

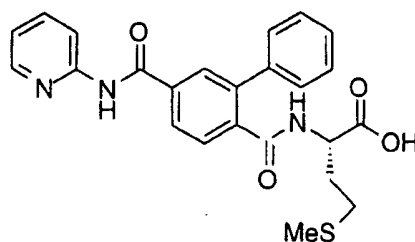
The resultant compound from Example 58A is hydrolyzed according to the procedure of Example 1B to give the title product.

5115

Example 59

naming error (S) Pyroglutamyl-(4-aminomethyl-2-phenyl)benzoyl methionine

- 5120 Using the procedure of Example 58 and replacing pyroglutamic acid with 3-pyridylacetic acid affords the title product.



5125

Example 60

4-[(Pyridin-2-ylamino)carbonyl]-2-phenylbenzoyl methionine

Example 60A

4-Carboxy-2-phenylbenzoyl methionine methyl ester

- 5130 A solution of 4-bromo-2-phenylbenzoyl methionine methyl ester (1.0 equivalent), Pd(OAc)₂ (0.05 equivalent) and DPPE (1.0 equivalent) is heated in DMF to 65° C under 4 atm. of carbon monoxide until TLC analysis indicates that the reaction is complete. The reaction mixture is poured into water and extracted with ethyl acetate which is dried and evaporated. The product is purified by chromatography on silica gel.

5135

Example 60B

4-[(Pyridin-2-ylamino)carbonyl]-2-phenylbenzoyl methionine methyl ester

- 5140 To a solution of the resultant acid from Example 60A (1.0 equivalent) in DMF is added 3-hydroxy-1,2,3-benzotriazin-4(3H)-one (1.5 equivalents) followed by 2-aminopyridine (1.0 equivalent) and 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (1.5 equivalents). When judged complete by TLC analysis, the reaction is taken up in ethyl acetate which is washed by 1N HCl and saturated brine, and then is dried and evaporated. The crude reaction mixture is purified by column chromatography to afford the title product.

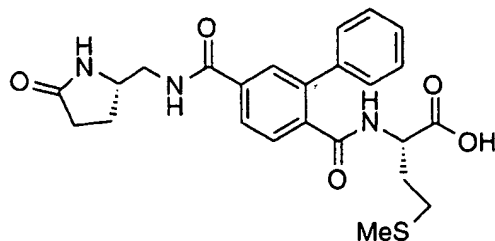
5145

Example 60C

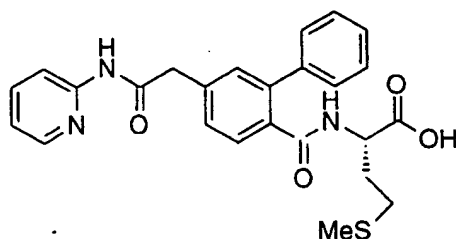
4-[(Pyridin-2-ylamino)carbonyl]-2-phenylbenzoyl methionine

The resultant compound from Example 60B is hydrolyzed according to the procedure of Example 1B to give the title product.

5150

Example 614-((S)-2-Pyrrolidone-5-aminomethyl)carbonyl-2-phenylbenzoyl methionine

Using the procedure of Example 60 and replacing 2-aminopyridine with (S)-5-aminomethyl-
 5155 2-pyrrolidone affords the title product.

Example 624-[(Pyridin-2-ylamino)carbonylmethyl]-2-phenylbenzoyl methionine

5160

Example 62A4-Diazocarbonyl-2-phenylbenzoyl methionine methyl ester

The resultant acid from Example 60A (1 equivalent) in dichloromethane is treated with
 5165 oxalyl chloride (1 equivalent) and DMF (0.05 equivalent). When gas evolution has ceased,
 the acid chloride solution is added to an ether solution of diazomethane. The reaction is
 stirred until judged complete by TLC analysis, and then is concentrated to give the crude title
 compound which is purified by chromatography on silica gel.

5170

Example 62B4-carboxymethyl-2-phenylbenzoyl methionine methyl ester

The resultant compound from Example 62A (1 equivalent) in dioxane is added to a slurry of
 sodium thiosulfate (1.1 equivalents) and silver (I) oxide (0.5 equivalent) in water. The
 reaction is stirred until judged complete by TLC analysis, filtered, acidified, and extracted
 5175 into ethyl acetate which is dried and evaporated. Chromatography of the residue on silica
 gel affords the title product.

Example 62C

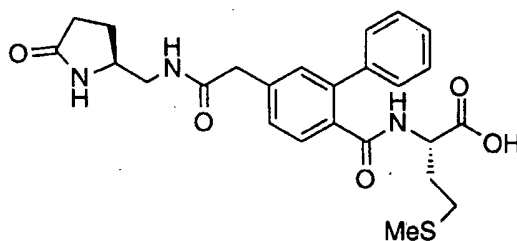
4-[(Pyridin-2-ylamino)carbonylmethyl]-2-phenylbenzoyl methionine methyl ester

5180 To a solution of the resultant acid from Example 62B (1.0 equivalent) in dimethylformamide (DMF) is added 3-hydroxy-1,2,3-benzotriazin-4(3H)-one (1.5 equivalents) followed by 2-aminopyridine (1.0 equivalent) and 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (1.5 equivalents). When judged complete by TLC analysis, the reaction is taken up in ethyl acetate which is washed with 1N HCl and saturated brine, and then is dried

5185 and evaporated. The crude reaction mixture is purified by column chromatography to afford the title product.

Example 62D4-[(Pyridin-2-ylamino)carbonylmethyl]-2-phenylbenzoyl methionine

5190 The resultant compound from Example 62C is hydrolyzed according to the procedure of Example 1B to give the title product.

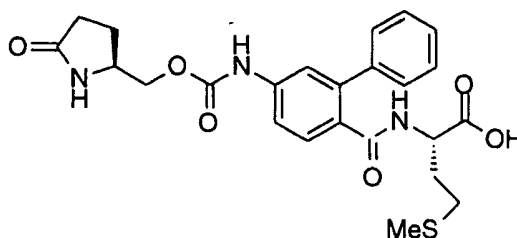


5195

Example 634-((S)-2-Pyrrolidone-5-aminomethyl)carbonylmethyl)-2-phenylbenzoyl methionine

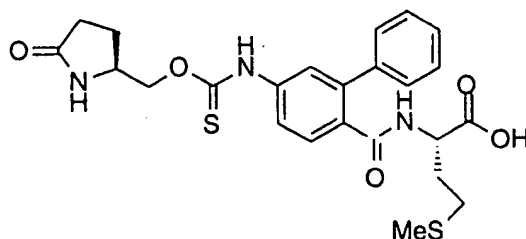
Using the procedure of Example 62 and replacing 2-aminopyridine with (S)-5-aminomethyl-2-pyrrolidone affords the title product.

5200

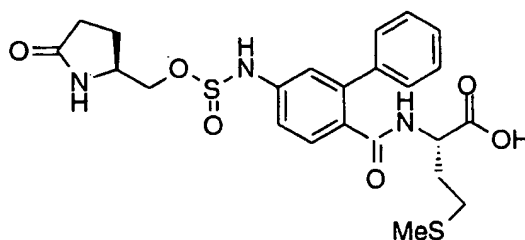
Example 644-((S)-2-Pyrrolidone-5-methoxycarbonylamino)-2-phenylbenzoyl methionine

The title compound is prepared as described in Example 1 with the exception that (S)-5-aminomethyl-2-pyrrolidone (1.0 equivalent) is replaced by (S)-5-hydroxymethyl-2-pyrrolidone (1.0 equivalent) and CuCl (0.1 equivalent).

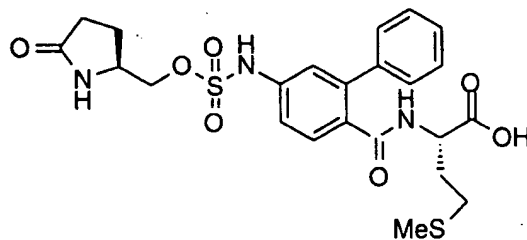
5205

Example 654-((S)-2-Pyrrolidone-5-methoxythiocarbonylamino-2-phenylbenzoyl methionine

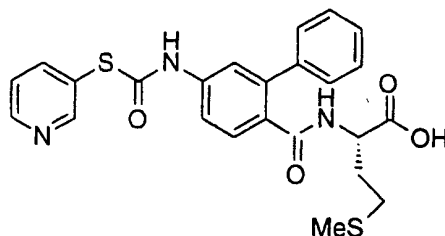
The title compound is prepared as described in Example 1 with the exception that (S)-5-aminomethyl-2-pyrrolidone (1.0 equivalent) is replaced by (S)-5-hydroxymethyl-2-pyrrolidone (1.0 equivalent) and CuCl (0.1 equivalent), and triphosgene (0.33 equivalent) is replaced by thiophosgene (1.0 equivalent).

Example 664-((S)-2-Pyrrolidone-5-methoxysulfinylamino-2-phenylbenzoyl methionine

The title compound is prepared as described in Example 3 with the exception that (S)-5-aminomethyl-2-pyrrolidone (1.0 equivalent) is replaced by (S)-5-hydroxymethyl-2-pyrrolidone (1.0 equivalent) and CuCl (0.1 equivalent).

Example 674-((S)-2-Pyrrolidone-5-methoxysulfonylamino-2-phenylbenzoyl methionine

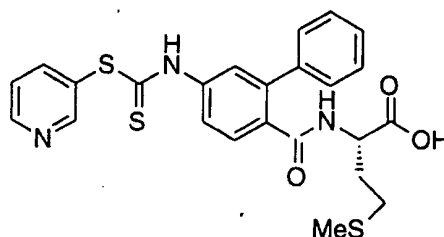
The title compound is prepared as described in Example 4 with the exception that (*S*)-5-aminomethyl-2-pyrrolidone (1.0 equivalent) is replaced by (*S*)-5-hydroxymethyl-2-pyrrolidone (1.0 equivalent) and CuCl (0.1 equivalent).



Example 68

4-(Pyridin-3-ylmercaptocarbonyl)amino-2-phenylbenzoyl methionine

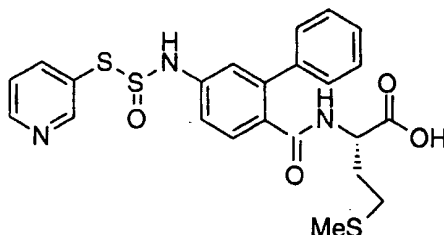
The title compound is prepared as described in Example 1 with the exception that (*S*)-5-aminomethyl-2-pyrrolidone (1.0 equivalent) is replaced by 3-mercaptopyridine (1.0 equivalent).



Example 69

4-(Pyridin-3-ylmercaptothiocarbonyl)amino-2-phenylbenzoyl methionine

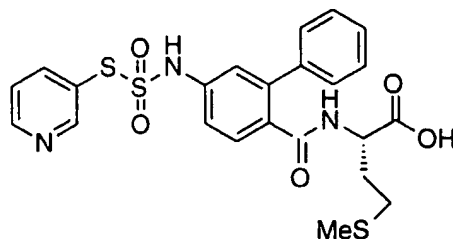
The title compound is prepared as described in Example 1 with the exception that (*S*)-5-aminomethyl-2-pyrrolidone (1.0 equivalent) is replaced by 3-mercaptopyridine (1.0 equivalent), and triphosgene (0.33 equivalent) is replaced by thiophosgene (1.0 equivalent).



Example 70

4-(Pyridin-3-ylmercaptosulfinyl)amino-2-phenylbenzoyl methionine

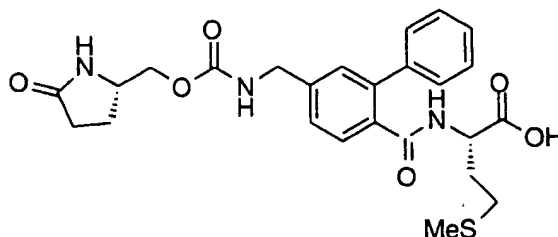
The title compound is prepared as described in Example 3 with the exception that (*S*)-5-aminomethyl-2-pyrrolidone (1.0 equivalent) is replaced by 3-mercaptopyridine (1.0 equivalent).



Example 71

4-(Pyridin-3-ylmercaptosulfonyl)amino-2-phenylbenzoyl methionine

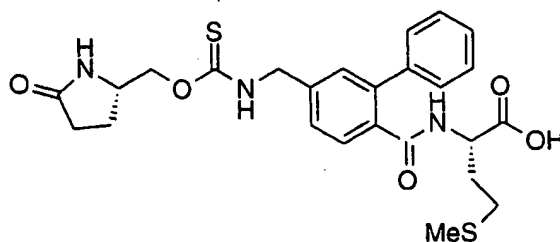
The title compound is prepared as described in Example 4 with the exception that (*S*)-5-aminomethyl-2-pyrrolidone (1.0 equivalent) is replaced by 3-mercaptopyridine (1.0 equivalent).



Example 72

4-((*S*)-2-Pyrrolidone-5-methoxycarbonyl)aminomethyl-2-phenylbenzoyl methionine

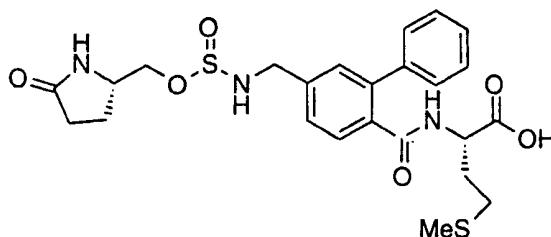
The title compound is prepared as described in Example 18 with the exception that (*S*)-5-aminomethyl-2-pyrrolidone (1.0 equivalent) is replaced by (*S*)-5-hydroxymethyl-2-pyrrolidone (1.0 equivalent) and CuCl (0.1 equivalent).



Example 73

4-((*S*)-2-Pyrrolidone-5-methoxythiocarbonyl)aminomethyl-2-phenylbenzoyl methionine

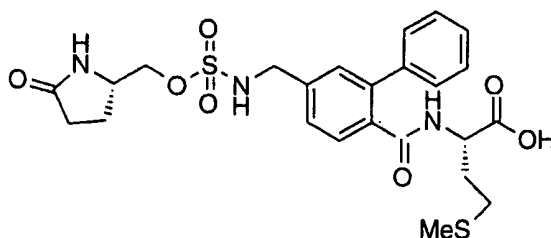
The title compound is prepared as described in Example 18 with the exception that (*S*)-5-aminomethyl-2-pyrrolidone (1.0 equivalent) is replaced by (*S*)-5-hydroxymethyl-2-pyrrolidone (1.0 equivalent) and CuCl (0.1 equivalent), and triphosgene (0.33 equivalent) is replaced by thiophosgene (1.0 equivalent).



Example 74

4-((*S*)-2-Pyrrolidone-5-methoxysulfinyl)aminomethyl-2-phenylbenzoyl methionine

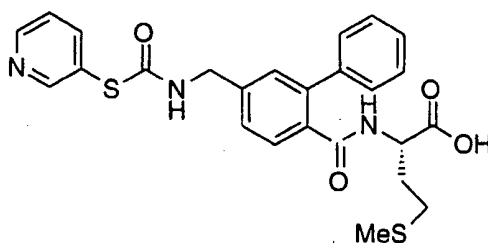
The title compound is prepared as described in Example 3 using the resultant amine from Example 18B with the exception that (*S*)-5-aminomethyl-2-pyrrolidone (1.0 equivalent) is replaced by (*S*)-5-hydroxymethyl-2-pyrrolidone (1.0 equivalent) and CuCl (0.1 equivalent).



Example 75

4-((*S*)-2-Pyrrolidone-5-methoxysulfonyl)aminomethyl-2-phenylbenzoyl methionine

The title compound is prepared as described in Example 4 using the resultant amine from Example 18B with the exception that (*S*)-5-aminomethyl-2-pyrrolidone (1.0 equivalent) is replaced by (*S*)-5-hydroxymethyl-2-pyrrolidone (1.0 equivalent) and CuCl (0.1 equivalent).

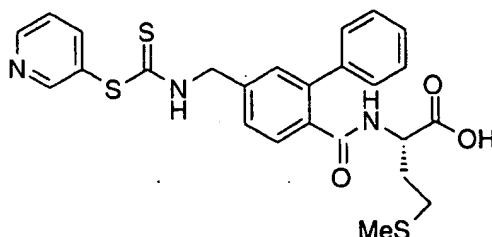


Example 76

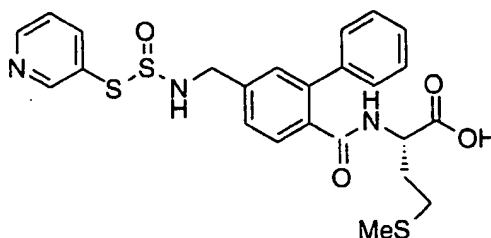
4-(Pyridin-3-yl)mercaptocarbonyl)aminomethyl-2-phenylbenzoyl methionine

The title compound is prepared as described in Example 18 with the exception that (*S*)-5-aminomethyl-2-pyrrolidone (1.0 equivalent) is replaced by 3-mercaptopyridine (1.0 equivalent).

5305

Example 774-(Pyridin-3-yl)mercaptosulfinyl)aminomethyl-2-phenylbenzoyl methionine

5310 The title compound is prepared as described in Example 18 with the exception that (*S*)-5-aminomethyl-2-pyrrolidone (1.0 equivalent) is replaced by 3-mercaptopyridine (1.0 equivalent), and triphosgene (0.33 equivalent) is replaced by thiophosgene (1.0 equivalent).

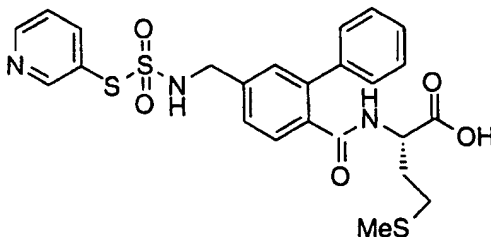


5315

Example 784-(Pyridin-3-yl)mercaptosulfinyl)aminomethyl-2-phenylbenzoyl methionine

The title compound is prepared as described in Example 3 using the resultant amine from Example 18B with the exception that (*S*)-5-aminomethyl-2-pyrrolidone (1.0 equivalent) is replaced by 3-mercaptopyridine (1.0 equivalent).

5320

Example 79

5325 4-(Pyridin-3-ylmercaptosulfonyl)aminomethyl-2-phenylbenzoyl methionine

The title compound is prepared as described in Example 4 using the resultant amine from Example 18B with the exception that (*S*)-5-aminomethyl-2-pyrrolidone (1.0 equivalent) is replaced by 3-mercaptopyridine (1.0 equivalent).

5330

Example 80A-NH-CO-NH-B

The procedure of Example 1 is used with the exception that 4-amino-2-phenylbenzoyl methionine methyl ester is replaced by an aniline from Table 1 (B-NH₂) and (*S*)-5-aminomethyl-2-pyrrolidone is replaced by an amine from Table 3 (A-NH₂). For products derived from amines 146-206 from Table 3, the final LiOH hydrolysis step also hydrolyzes the ester on the fragment of the final compound that is derived from amines 146-206.

This example also encompasses compounds comprising a C-terminal ester moiety, in which case the final LiOH step is eliminated and the amino acid methyl esters used to prepare the anilines in Table 1 are replaced by the corresponding ethyl, propyl, isopropyl, butyl, sec-butyl, isobutyl, isoamyl, hexyl, octyl, cyclohexyl or phenethyl esters.

5340

Example 81A-NH-CS-NH-B

5345

The procedure of Example 1 is used with the exception that triphosgene (0.33 equivalent) is replaced by thiophosgene (1.0 equivalent), 4-amino-2-phenylbenzoyl methionine methyl ester is replaced by an aniline from Table 1 (B-NH₂) and (*S*)-5-aminomethyl-2-pyrrolidone is replaced by an amine from Table 3 (A-NH₂). For products derived from amines 146-206 from Table 3, the final LiOH hydrolysis step also hydrolyzes the ester on the fragment of the final compound that is derived from amines 146-206.

5350

This example also encompasses compounds comprising a C-terminal ester moiety, in which case the final LiOH step is eliminated and the amino acid methyl esters used to prepare the anilines in Table 1 are replaced by the corresponding ethyl, propyl, isopropyl, butyl, sec-butyl, isobutyl, isoamyl, hexyl, octyl, cyclohexyl or phenethyl esters.

5355

Example 82A-NH-SO-NH-B

The procedure of Example 3 is used with the exception that 4-amino-2-phenylbenzoyl methionine methyl ester is replaced by an aniline from Table 1 (B-NH₂) and (*S*)-5-

5360

aminomethyl-2-pyrrolidone is replaced by an amine from Table 3 (A-NH₂). For products derived from amines 146-206 from Table 3, the final LiOH hydrolysis step also hydrolyzes the ester on the fragment of the final compound that is derived from amines 146-206.

5365 This example also encompasses compounds comprising a C-terminal ester moiety, in which case the final LiOH step is eliminated and the amino acid methyl esters used to prepare the anilines in Table 1 are replaced by the corresponding ethyl, propyl, isopropyl, butyl, sec-butyl, isobutyl, isoamyl, hexyl, octyl, cyclohexyl or phenethyl esters.

5370

Example 83

A-NH-SO₂-NH-B

The procedure of Example 4 is used with the exception that 4-amino-2-phenylbenzoyl methionine methyl ester is replaced by an aniline from Table 1 (B-NH₂) and
5375 (*S*)-5-aminomethyl-2-pyrrolidone is replaced by an amine from Table 3 (A-NH₂). For products derived from amines 146-206 from Table 3, the final LiOH hydrolysis step also hydrolyzes the ester on the fragment of the final compound that is derived from amines 146-206.

5380 This example also encompasses compounds comprising a C-terminal ester moiety, in which case the final LiOH step is eliminated and the amino acid methyl esters used to prepare the anilines in Table 1 are replaced by the corresponding ethyl, propyl, isopropyl, butyl, sec-butyl, isobutyl, isoamyl, hexyl, octyl, cyclohexyl or phenethyl esters.

5385

Example 84

A-NH-SO₂-B

The procedure of Example 5 is used with the exception that 4-amino-2-phenylbenzoyl methionine methyl ester is replaced by an aniline from Table 1 (B-NH₂) and (*S*)-5-aminomethyl-2-pyrrolidone is replaced by an amine from Table 3 (A-NH₂). For products
5390 derived from amines 146-206 from Table 3, the final LiOH hydrolysis step also hydrolyzes the ester on the fragment of the final compound that is derived from amines 146-206.

This example also encompasses compounds comprising a C-terminal ester moiety, in which case the final LiOH step is eliminated and the amino acid methyl esters used to prepare the anilines in Table 1 are replaced by the corresponding ethyl, propyl, isopropyl, butyl, sec-
5395 butyl, isobutyl, isoamyl, hexyl, octyl, cyclohexyl or phenethyl esters.

Example 85

A-NH-CO-O-B

The anilines from Table 1 (B-NH₂) are reacted according to the procedure of Example 6E.
5400 The resultant phenols are reacted according to the procedure of Example 8 with the exception that (S)-5-aminomethyl-2-pyrrolidone is replaced by an amine from Table 3 (A-NH₂). For products derived from amines 146-206 from Table 3, the final LiOH hydrolysis step also hydrolyzes the ester on the fragment of the final compound that is derived from amines 146-206.
5405 This example also encompasses compounds comprising a C-terminal ester moiety, in which case the final LiOH step is eliminated and the amino acid methyl esters used to prepare the anilines in Table 1 are replaced by the corresponding ethyl, propyl, isopropyl, butyl, sec-butyl, isobutyl, isoamyl, hexyl, octyl, cyclohexyl or phenethyl esters.

5410

Example 86A-NH-CS-O-B

The anilines from Table 1 (B-NH₂) are reacted according to the procedure of Example 6E. The resultant phenols are reacted according to the procedure of Example 8 with the exception that phosgene in toluene is replaced by thiophosgene and (S)-5-aminomethyl-2-pyrrolidone is replaced by an amine from Table 3 (A-NH₂). For products
5415 derived from amines 146-206 from Table 3, the final LiOH hydrolysis step also hydrolyzes the ester on the fragment of the final compound that is derived from amines 146-206. This example also encompasses compounds comprising a C-terminal ester moiety, in which case the final LiOH step is eliminated and the amino acid methyl esters used to prepare the anilines in Table 1 are replaced by the corresponding ethyl, propyl, isopropyl, butyl, sec-butyl, isobutyl, isoamyl, hexyl, octyl, cyclohexyl or phenethyl esters.
5420

5425

Example 87A-NH-SO-O-B

The anilines from Table 1 (B-NH₂) are reacted according to the procedure of Example 6E. The resultant phenols are reacted according to the procedure of Example 8 with the exception that phosgene in toluene is replaced by thionyl chloride and (S)-5-aminomethyl-2-pyrrolidone is replaced by an amine from Table 3 (A-NH₂). For products derived from
5430 amines 146-206 from Table 3, the final LiOH hydrolysis step also hydrolyzes the ester on the fragment of the final compound that is derived from amines 146-206. This example also encompasses compounds comprising a C-terminal ester moiety, in which case the final LiOH step is eliminated and the amino acid methyl esters used to prepare the anilines in Table 1 are replaced by the corresponding ethyl, propyl, isopropyl, butyl, sec-butyl, isobutyl, isoamyl, hexyl, octyl, cyclohexyl or phenethyl esters.
5435

Example 88A-NH-SO₂-O-B

5440 The anilines from Table 1 (B-NH₂) are reacted according to the procedure of Example 6E. The resultant phenols are reacted according to the procedure of Example 8 with the exception that phosgene in toluene is replaced by sulfuryl chloride and (*S*)-5-aminomethyl-2-pyrrolidone is replaced by an amine from Table 3 (A-NH₂). For products derived from amines 146-206 from Table 3, the final LiOH hydrolysis step also hydrolyzes
5445 the ester on the fragment of the final compound that is derived from amines 146-206.

This example also encompasses compounds comprising a C-terminal ester moiety, in which case the final LiOH step is eliminated and the amino acid methyl esters used to prepare the anilines in Table 1 are replaced by the corresponding ethyl, propyl, isopropyl, butyl, sec-butyl, isobutyl, isoamyl, hexyl, octyl, cyclohexyl or phenethyl esters.

5450

Example 89A-NH-CH₂-B

The procedure of Example 16 is used with the exception that (2-phenyl-4-bromobenzoyl)-methionine methyl ester is replaced by a bromide from Table 2 (B-Br) and 2-aminopyridine
5455 is replaced by an amine from Table 3 (A-NH₂). For products derived from amines 146-206 from Table 3, the final LiOH hydrolysis step also hydrolyzes the ester on the fragment of the final compound that is derived from amines 146-206.

This example also encompasses compounds comprising a C-terminal ester moiety, in which
5460 case the final LiOH step is eliminated and the amino acid methyl esters used to prepare the bromides in Table 2 are replaced by the corresponding ethyl, propyl, isopropyl, butyl, sec-butyl, isobutyl, isoamyl, hexyl, octyl, cyclohexyl or phenethyl esters.

5465

Example 90A-NH-CO-NH-CH₂-B

The bromides from Table 2 (B-Br) are reacted according to the procedures of Example 16F-G. The resultant alcohols are reacted according to the procedure of Example 18 with the exception that (*S*)-5-aminomethyl-2-pyrrolidone is replaced by an amine from
5470 Table 3 (A-NH₂). For products derived from amines 146-206 from Table 3, the final LiOH hydrolysis step also hydrolyzes the ester on the fragment of the final compound that is derived from amines 146-206.

This example also encompasses compounds comprising a C-terminal ester moiety, in which case the final LiOH step is eliminated and the amino acid methyl esters used to prepare the bromides in Table 2 are replaced by the corresponding ethyl, propyl, isopropyl, butyl, sec-butyl, isobutyl, isoamyl, hexyl, octyl, cyclohexyl or phenethyl esters.

Example 91

A-NH-CS-NH-CH₂-B

The bromides from Table 2 (B-Br) are reacted according to the procedures of Example 16F-G. The resultant alcohols are reacted according to the procedure of Example 18 with the exception that triphosgene (0.33 equivalent) is replaced by thiophosgene (1.0 equivalent) and (S)-5-aminomethyl-2-pyrrolidone is replaced by an amine from Table 3 (A-NH₂). For products derived from amines 146-206 from Table 3, the final LiOH hydrolysis step also hydrolyzes the ester on the fragment of the final compound that is derived from amines 146-206.

This example also encompasses compounds comprising a C-terminal ester moiety, in which case the final LiOH step is eliminated and the amino acid methyl esters used to prepare the bromides in Table 2 are replaced by the corresponding ethyl, propyl, isopropyl, butyl, sec-butyl, isobutyl, isoamyl, hexyl, octyl, cyclohexyl or phenethyl esters.

Example 92

A-NH-SO-NH-CH₂-B

The bromides from Table 2 (B-Br) are reacted according to the procedures of Example 16F-G. The resultant alcohols are reacted according to the procedure of Example 18 with the exception that triphosgene (0.33 equivalent) is replaced by thionyl chloride (1.0 equivalent) and (S)-5-aminomethyl-2-pyrrolidone is replaced by an amine from Table 3 (A-NH₂). For products derived from amines 146-206 from Table 3, the final LiOH hydrolysis step also hydrolyzes the ester on the fragment of the final compound that is derived from amines 146-206.

This example also encompasses compounds comprising a C-terminal ester moiety, in which case the final LiOH step is eliminated and the amino acid methyl esters used to prepare the bromides in Table 2 are replaced by the corresponding ethyl, propyl, isopropyl, butyl, sec-butyl, isobutyl, isoamyl, hexyl, octyl, cyclohexyl or phenethyl esters.

Example 93

A-NH-SO₂-NH-CH₂-B

5510 The bromides from Table 2 (B-Br) are reacted according to the procedures of Example 16F-G. The resultant alcohols are reacted according to the procedure of Example 18 with the exception that triphosgene (0.33 equivalent) is replaced by sulfuryl chloride (1.0 equivalent) and (*S*)-5-aminomethyl-2-pyrrolidone is replaced by an amine from Table 3 (A-NH₂). For products derived from amines 146-206 from Table 3, the final LiOH hydrolysis step also
5515 hydrolyzes the ester on the fragment of the final compound that is derived from amines 146-206.

This example also encompasses compounds comprising a C-terminal ester moiety, in which case the final LiOH step is eliminated and the amino acid methyl esters used to prepare the bromides in Table 2 are replaced by the corresponding ethyl, propyl, isopropyl,
5520 butyl, sec-butyl, isobutyl, isoamyl, hexyl, octyl, cyclohexyl or phenethyl esters.

Example 94

A-NH-CO-O-CH₂-B

5525 The bromides from Table 2 (B-Br) are reacted according to the procedures of Example 16F-G. The resultant alcohols are reacted according to the procedure of Example 8 with the exception that (*S*)-5-aminomethyl-2-pyrrolidone is replaced by an amine from Table 3 (A-NH₂). For products derived from amines 146-206 from Table 3, the final LiOH hydrolysis step also hydrolyzes the ester on the fragment of the final compound that is derived from
5530 amines 146-206.

This example also encompasses compounds comprising a C-terminal ester moiety, in which case the final LiOH step is eliminated and the amino acid methyl esters used to prepare the bromides in Table 2 are replaced by the corresponding ethyl, propyl, isopropyl, butyl, sec-butyl, isobutyl, isoamyl, hexyl, octyl, cyclohexyl or phenethyl esters.

5535

Example 95

A-NH-CS-O-CH₂-B

The bromides from Table 2 (B-Br) are reacted according to the procedures of Example 16F-G. The resultant alcohols are reacted according to the procedure of Example 8 with the
5540 exception that phosgene in toluene is replaced by thiophosgene and (*S*)-5-aminomethyl-2-pyrrolidone is replaced by an amine from Table 3 (A-NH₂). For products derived from amines 146-206 from Table 3, the final LiOH hydrolysis step also hydrolyzes the ester on the fragment of the final compound that is derived from amines 146-206.

This example also encompasses compounds comprising a C-terminal ester moiety, in which
5545 case the final LiOH step is eliminated and the amino acid methyl esters used to prepare the

bromides in Table 2 are replaced by the corresponding ethyl, propyl, isopropyl, butyl, sec-butyl, isobutyl, isoamyl, hexyl, octyl, cyclohexyl or phenethyl esters.

Example 96

A-NH-CO-S-B

5550

The anilines Table 1 (B-NH₂) are converted into the corresponding mercaptans according to the procedure of Example 12E. These mercaptans are reacted according to the procedure of Example 29 with the exception that 2-aminothiazol is replaced by an amine from Table 3 (A-NH₂). For products derived from amines 146-206 from Table 3, the final LiOH hydrolysis

5555 step also hydrolyzes the ester on the fragment of the final compound that is derived from amines 146-206.

This example also encompasses compounds comprising a C-terminal ester moiety, in which case the final LiOH step is eliminated and the amino acid methyl esters used to prepare the anilines in Table 1 are replaced by the corresponding ethyl, propyl, isopropyl, butyl, sec-

5560 butyl, isobutyl, isoamyl, hexyl, octyl, cyclohexyl or phenethyl esters.

Example 97

A-NH-CS-S-B

5565

The anilines Table 1 (B-NH₂) are converted into the corresponding mercaptans according to the procedure of Example 12E. These mercaptans are reacted according to the procedure of Example 29 with the exception that phosgene in toluene is replaced by thiophosgene and 2-aminothiazol is replaced by an amine from Table 3 (A-NH₂). For products derived from amines 146-206 from Table 3, the final LiOH hydrolysis step also hydrolyzes the ester on

5570 the fragment of the final compound that is derived from amines 146-206.

This example also encompasses compounds comprising a C-terminal ester moiety, in which case the final LiOH step is eliminated and the amino acid methyl esters used to prepare the anilines in Table 1 are replaced by the corresponding ethyl, propyl, isopropyl, butyl, sec-butyl, isobutyl, isoamyl, hexyl, octyl, cyclohexyl or phenethyl esters.

5575

Example 98

A-NH-SO-S-B

5580

The anilines Table 1 (B-NH₂) are converted into the corresponding mercaptans according to the procedure of Example 12E. These mercaptans are reacted according to the procedure of Example 29 with the exception that phosgene in toluene is replaced by thionyl chloride and 2-aminothiazol is replaced by an amine from Table 3 (A-NH₂). For products derived from

amines 146-206 from Table 3, the final LiOH hydrolysis step also hydrolyzes the ester on the fragment of the final compound that is derived from amines 146-206.

5585 This example also encompasses compounds comprising a C-terminal ester moiety, in which case the final LiOH step is eliminated and the amino acid methyl esters used to prepare the anilines in Table 1 are replaced by the corresponding ethyl, propyl, isopropyl, butyl, sec-butyl, isobutyl, isoamyl, hexyl, octyl, cyclohexyl or phenethyl esters.

5590

Example 99

A-NH-SO₂-S-B

The anilines Table 1 (B-NH₂) are converted into the corresponding mercaptans according to the procedure of Example 12E. These mercaptans are reacted according to the procedure of

5595 Example 29 with the exception that phosgene in toluene is replaced by sulfur chloride and 2-aminothiazol is replaced by an amine from Table 3 (A-NH₂). For products derived from amines 146-206 from Table 3, the final LiOH hydrolysis step also hydrolyzes the ester on the fragment of the final compound that is derived from amines 146-206.

This example also encompasses compounds comprising a C-terminal ester moiety, in which

5600 case the final LiOH step is eliminated and the amino acid methyl esters used to prepare the anilines in Table 1 are replaced by the corresponding ethyl, propyl, isopropyl, butyl, sec-butyl, isobutyl, isoamyl, hexyl, octyl, cyclohexyl or phenethyl esters.

5605

Example 100

A-NH-CO-S-CH₂-B

The bromides from Table 2 (B-Br) are reacted according to the procedures of Example 16F-G. The resultant alcohols are converted to the corresponding mercaptans according to the procedures of Examples 27A and 37A. These mercaptans are reacted according to the

5610 procedure of Example 29 with the exception that 2-aminothiazol is replaced by an amine from Table 3 (A-NH₂). For products derived from amines 146-206 from Table 3, the final LiOH hydrolysis step also hydrolyzes the ester on the fragment of the final compound that is derived from amines 146-206.

This example also encompasses compounds comprising a C-terminal ester moiety, in which

5615 case the final LiOH step is eliminated and the amino acid methyl esters used to prepare the anilines in Table 1 are replaced by the corresponding ethyl, propyl, isopropyl, butyl, sec-butyl, isobutyl, isoamyl, hexyl, octyl, cyclohexyl or phenethyl esters.

5620

Example 101A-NH-CS-S-CH₂-B

5625

The bromides from Table 2 (B-Br) are reacted according to the procedures of Example 16F-G. The resultant alcohols are converted to the corresponding mercaptans according to the procedures of Examples 27A and 37A. These mercaptans are reacted according to the procedure of Example 29 with the exception that phosgene in toluene is replaced by thiophosgene and 2-aminothiazol is replaced by an amine from Table 3 (A-NH₂). For products derived from amines 146-206 from Table 3, the final LiOH hydrolysis step also hydrolyzes the ester on the fragment of the final compound that is derived from amines 146-206.

5630

This example also encompasses compounds comprising a C-terminal ester moiety, in which case the final LiOH step is eliminated and the amino acid methyl esters used to prepare the bromides in Table 2 are replaced by the corresponding ethyl, propyl, isopropyl, butyl, sec-butyl, isobutyl, isoamyl, hexyl, octyl, cyclohexyl or phenethyl esters.

5635

Example 102A-NH-SO-S-CH₂-B

5640

The bromides from Table 2 (B-Br) are reacted according to the procedures of Example 16F-G. The resultant alcohols are converted to the corresponding mercaptans according to the procedures of Examples 27A and 37A. These mercaptans are reacted according to the procedure of Example 29 with the exception that phosgene in toluene is replaced by thionyl chloride and 2-aminothiazol is replaced by an amine from Table 3 (A-NH₂). For products derived from amines 146-206 from Table 3, the final LiOH hydrolysis step also hydrolyzes the ester on the fragment of the final compound that is derived from amines 146-206.

This example also encompasses compounds comprising a C-terminal ester moiety, in which case the final LiOH step is eliminated and the amino acid methyl esters used to prepare the bromides in Table 2 are replaced by the corresponding ethyl, propyl, isopropyl, butyl, sec-butyl, isobutyl, isoamyl, hexyl, octyl, cyclohexyl or phenethyl esters.

5650

Example 103A-NH-SO₂-S-CH₂-B

5655

The bromides from Table 2 (B-Br) are reacted according to the procedures of Example 16F-G. The resultant alcohols are converted to the corresponding mercaptans according to the procedures of Examples 27A and 37A. These mercaptans are reacted according to the procedure of Example 29 with the exception that phosgene in toluene is replaced by sulfuryl

chloride and 2-aminothiazol is replaced by an amine from Table 3 (A-NH₂). For products derived from amines 146-206 from Table 3, the final LiOH hydrolysis step also hydrolyzes the ester on the fragment of the final compound that is derived from amines 146-206.

5660 example also encompasses compounds comprising a C-terminal ester moiety, in which case the final LiOH step is eliminated and the amino acid methyl esters used to prepare the bromides in Table 2 are replaced by the corresponding ethyl, propyl, isopropyl, butyl, sec-butyl, isobutyl, isoamyl, hexyl, octyl, cyclohexyl or phenethyl esters.

5665

Example 104

A-CO-NH-B

The procedure of Example 56 is used with the exception that 4-amino-2-phenylbenzoyl methionine methyl ester is replaced by an aniline from Table 1 (B-NH₂) and pyroglutamic acid is replaced by an acid from Table 4 (A-CO₂H). For products derived from acids 164-
5670 238 and 262-269 from Table 4, the LiOH hydrolysis step is followed by removal of the tert-butyloxycarbonyl (Boc) amine protecting group by stirring the resultant compound from the LiOH hydrolysis step in a 1:1 mixture of dichloromethane and trifluoroacetic acid until TLC analysis indicates that the reaction is complete. The solvent is evaporated and the residue is purified by chromatography on silica gel.

5675 This example also encompasses compounds comprising a C-terminal ester moiety, in which case the final LiOH step is eliminated and the amino acid methyl esters used to prepare the anilines in Table 1 are replaced by the corresponding ethyl, propyl, isopropyl, butyl, sec-butyl, isobutyl, isoamyl, hexyl, octyl, cyclohexyl or phenethyl esters.

5680

Example 105

A-CO-NH-CH₂-B

The bromides from Table 2 (B-Br) are reacted according to the procedures of Example 16F-G. The resultant alcohols are converted to the corresponding amines according to the
5685 procedures of Examples 18A-B. These amines are reacted according to the procedure of Example 58 with the exception that pyroglutamic acid is replaced by an acid from Table 4 (A-CO₂H). For products derived from acids 164-238 and 262-269 from Table 4, the LiOH hydrolysis step is followed by removal of the tert-butyloxycarbonyl (Boc) amine protecting group by stirring the resultant compound from the LiOH hydrolysis step in a 1:1 mixture of
5690 dichloromethane and trifluoroacetic acid until TLC analysis indicates that the reaction is complete. The solvent is evaporated and the residue is purified by chromatography on silica gel.

This example also encompasses compounds comprising a C-terminal ester moiety, in which case the final LiOH step is eliminated and the amino acid methyl esters used to prepare the bromides in Table 2 are replaced by the corresponding ethyl, propyl, isopropyl, butyl, sec-butyl, isobutyl, isoamyl, hexyl, octyl, cyclohexyl or phenethyl esters.

Example 106

A-CO-C \equiv C-B

The bromides from Table 2 (B-Br) are reacted according to the procedure of Example 47A. The resultant acetylenes are reacted according to the procedure of Example 53 with the exception that 1-methyl-4-imidazoleacetic acid is replaced by an acid from Table 4 (A-CO₂H). For products derived from acids 164-238 and 262-269 from Table 4, the LiOH hydrolysis step is followed by removal of the tert-butyloxycarbonyl (Boc) amine protecting group by stirring the resultant compound from the LiOH hydrolysis step in a 1:1 mixture of dichloromethane and trifluoroacetic acid until TLC analysis indicates that the reaction is complete. The solvent is evaporated and the residue is purified by chromatography on silica gel.

This example also encompasses compounds comprising a C-terminal ester moiety, in which case the final LiOH step is eliminated and the amino acid methyl esters used to prepare the bromides in Table 2 are replaced by the corresponding ethyl, propyl, isopropyl, butyl, sec-butyl, isobutyl, isoamyl, hexyl, octyl, cyclohexyl or phenethyl esters.

Example 107

A-CO-CH=CH-B

The products from Example 106 are reacted according to the procedure of Example 54. This example also encompasses compounds comprising a C-terminal ester moiety, in which case the final LiOH step is eliminated and the amino acid methyl esters used to prepare the bromides in Table 2 are replaced by the corresponding ethyl, propyl, isopropyl, butyl, sec-butyl, isobutyl, isoamyl, hexyl, octyl, cyclohexyl or phenethyl esters.

Example 108

A-CO-CH₂-CH₂-B

The products from Example 107 are reacted according to the procedure of Example 55. This example also encompasses compounds comprising a C-terminal ester moiety, in which case the final LiOH step is eliminated and the amino acid methyl esters used to prepare the

5730 bromides in Table 2 are replaced by the corresponding ethyl, propyl, isopropyl, butyl, sec-butyl, isobutyl, isoamyl, hexyl, octyl, cyclohexyl or phenethyl esters.

Example 109

5735

A-NH-CO-B

The procedure of Example 60 is used with the exception that 4-bromo-2-phenylbenzoyl methionine methyl ester is replaced by a bromide from Table 2 (B-Br) and 2-aminopyridine is replaced by an amine from Table 3 (A-NH₂). For products derived from amines 146-206 from Table 3, the final LiOH hydrolysis step also hydrolyzes the ester on the fragment of the final compound that is derived from amines 146-206.

5740

This example also encompasses compounds comprising a C-terminal ester moiety, in which case the final LiOH step is eliminated and the amino acid methyl esters used to prepare the bromides in Table 2 are replaced by the corresponding ethyl, propyl, isopropyl, butyl, sec-butyl, isobutyl, isoamyl, hexyl, octyl, cyclohexyl or phenethyl esters.

5745

Example 110

A-NH-CO-CH₂-B

The bromides from Table 2 (B-Br) are reacted according to the procedure of Example 60A.

5750

The resultant carbocyclic acids are reacted according to the procedure of Example 62 with the exception that 2-aminopyridine is replaced by an amine from Table 3 (A-NH₂). For products derived from amines 146-206 from Table 3, the final LiOH hydrolysis step also hydrolyzes the ester on the fragment of the final compound that is derived from amines 146-206.

5755

This example also encompasses compounds comprising a C-terminal ester moiety, in which case the final LiOH step is eliminated and the amino acid methyl esters used to prepare the bromides in Table 2 are replaced by the corresponding ethyl, propyl, isopropyl, butyl, sec-butyl, isobutyl, isoamyl, hexyl, octyl, cyclohexyl or phenethyl esters.

5760

Example 111

A-CH₂-NH-B

The procedure of Example 25 is used with the exception that 4-amino-2-phenylbenzoyl methionine methyl ester is replaced by an amine from Table 1 (B-NH₂) and 3-pyridinecarboxaldehyde is replaced by an aldehyde from Table 5 (A-CHO). For products derived from aldehydes 360-432 and 433-440 from Table 5, the LiOH hydrolysis step is

5765

followed by removal of the tert-butyloxycarbonyl (Boc) amine protecting group by stirring the resultant compound from the LiOH hydrolysis step in a 1:1 mixture of dichloromethane and trifluoroacetic acid until TLC analysis indicates that the reaction is complete. The solvent is evaporated and the residue is purified by chromatography on silica gel.

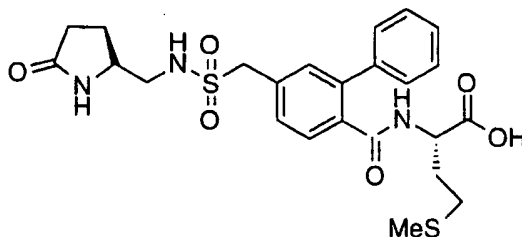
This example also encompasses compounds comprising a C-terminal ester moiety, in which case the final LiOH step is eliminated and the amino acid methyl esters used to prepare the anilines in Table 1 are replaced by the corresponding ethyl, propyl, isopropyl, butyl, sec-butyl, isobutyl, isoamyl, hexyl, octyl, cyclohexyl or phenethyl esters.

Example 112

A-CH₂-NH-CH₂-B

The bromides from Table 2 (B-Br) are reacted according to the procedures of Example 16F-G. The resultant alcohols are converted to the corresponding amines according to the procedures of Examples 18A-B. These amines are reacted according to the procedure of Example 25 with the exception that 3-pyridinecarboxaldehyde is replaced by an aldehyde from Table 5 (A-CHO). For products derived from aldehydes 360-432 and 433-440 from Table 5, the LiOH hydrolysis step is followed by removal of the tert-butyloxycarbonyl (Boc) amine protecting group by stirring the resultant compound from the LiOH hydrolysis step in a 1:1 mixture of dichloromethane and trifluoroacetic acid until TLC analysis indicates that the reaction is complete. The solvent is evaporated and the residue is purified by chromatography on silica gel.

This example also encompasses compounds comprising a C-terminal ester moiety, in which case the final LiOH step is eliminated and the amino acid methyl esters used to prepare the bromides in Table 2 are replaced by the corresponding ethyl, propyl, isopropyl, butyl, sec-butyl, isobutyl, isoamyl, hexyl, octyl, cyclohexyl or phenethyl esters.



Example 113

4-((S)-2-Pyrrolidone-5-aminomethyl)sulfonylmethyl)-2-phenylbenzoyl methionine

Example 113A5800 4-Thioacetoxymethyl-2-phenylbenzoic acid methyl ester

To triphenylphosphine (1.2 equivalents) in THF at -78 °C is added diethylazodicarboxylate (1.2 equivalents) in THF. After 10 min thiolacetic acid (1.3 equivalents) in THF is added followed by the resultant compound from Example 16B (1.1 equivalent) in THF. The reaction is stirred at -78 °C for 1 h and then at ambient temperature until it is judged to be complete by TLC analysis. The mixture is evaporated and the residue is taken up in methanol and is treated with K₂CO₃ (2 equivalents). When the reaction is judged to be complete by TLC analysis, the solvent is evaporated and the residue is chromatographed on silica gel to afford the title product.

5810 Example 113B4-Chlorosulfonylmethylene-2-phenylbenzoic acid methyl ester

The resultant compound from Example 113A in water is stirred vigorously while gaseous chlorine is bubbled through the mixture. When the reaction is judged to be done by TLC analysis, the reaction is extracted with dichloromethane which is dried and evaporated to afford the title product.

Example 113C4-((S)-2-Pyrrolidone-5-aminomethyl)sulfonylmethylene-2-phenylbenzoic acid methyl ester

5820 To a solution of the resultant compound from Example 113B (1.0 equivalent) in methylene chloride is added (S)-5-aminomethyl-2-pyrrolidone (1.0 equivalent) and triethylamine (1.0 equivalent). When the reaction is judged complete by TLC analysis, the solvent is evaporated and the residue is purified by chromatography on silica gel.

Example 113D5825 4-((S)-2-Pyrrolidone-5-aminomethyl)sulfonylmethylene-2-phenylbenzoic acid

The resultant compound from Example 113C is hydrolyzed according to the procedure of Example 1B to give the title product.

Example 113E5830 4-((S)-2-Pyrrolidone-5-aminomethyl)sulfonylmethylene-2-phenylbenzoyl methionine methyl ester

To a solution of the resultant compound from Example 113D (1.0 equivalent) in dimethylformamide (DMF) is added 3-hydroxy-1,2,3-benzotriazin-4(3H)-one (1.5 equivalents) followed by methionine methyl ester (1.0 equivalent) and 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (1.5 equivalents). When judged

complete by TLC analysis, the reaction is taken up in ethyl acetate which is washed with 1N HCl and saturated brine, and then is dried and evaporated. The crude reaction mixture is purified by column chromatography to afford the title product.

5840

Example 113F4-((S)-2-Pyrrolidone-5-aminomethyl)sulfonylmethylene-2-phenylbenzoyl methionine

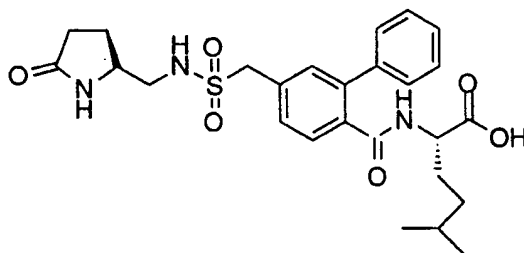
The resultant compound from Example 113E is hydrolyzed according to the procedure of Example 1B to give the title product.

5845

Example 114A-NH-SO₂-CH₂-B

The procedure of Example 113 is used with the exception that (S)-5-aminomethyl-2-pyrrolidone is replaced by an amine from Table 3 (A-NH₂). For products derived from amines 146-206 from Table 3, the final LiOH hydrolysis step also hydrolyzes the ester on the fragment of the final compound that is derived from amines 146-206.

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Example 1154-((S)-2-Pyrrolidone-5-aminomethyl)sulfonylmethyl)-2-phenylbenzoyl leucineExample 115A4-(Hydroxymethyl)-2-phenylbenzoyl leucine methyl ester

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(2-phenyl-4-bromobenzoyl)-leucine methyl ester is reacted according to the procedures of Example 16F-G.

Example 115B4-Thioacetoxymethyl)-2-phenylbenzoyl leucine methyl ester

5865

To triphenylphosphine (1.2 equivalents) in THF at -78 °C is added diethylazodicarboxylate (1.2 equivalents) in THF. After 10 min thioacetic acid (1.3 equivalents) in THF is added followed by the resultant compound from Example 115A (1. equivalent) in THF. The

reaction is stirred at -78 °C for 1 h and then at ambient temperature until it is judged to be complete by TLC analysis. The mixture is evaporated and the residue is taken up in methanol and is treated with K₂CO₃ (2 equivalents). When the reaction is judged to be complete by TLC analysis, the solvent is evaporated and the residue is chromatographed on silica gel to afford the title product.

Example 115C

4-Chlorosulfonylmethylene-2-phenylbenzoyl leucine methyl ester

The resultant compound from Example 115B in water is stirred vigorously while gaseous chlorine is bubbled through the mixture. When the reaction is judged to be done by TLC analysis, the reaction is extracted with dichloromethane which is dried and evaporated to afford the title product.

Example 115D

4-((S)-2-Pyrrolidone-5-aminomethyl)sulfonylmethylene-2-phenylbenzoyl leucine methyl ester

To a solution of the resultant compound from Example 115C (1.0 equivalent) in methylene chloride is added (S)-5-aminomethyl-2-pyrrolidone (1.0 equivalent) and triethylamine (1.0 equivalent). When the reaction is judged complete by TLC analysis, the solvent is evaporated and the residue is purified by chromatography on silica gel.

Example 115E

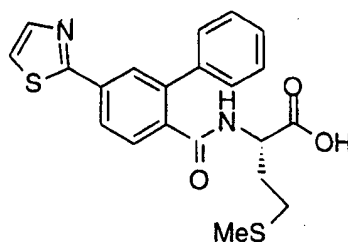
4-((S)-2-Pyrrolidone-5-aminomethyl)sulfonylmethylene-2-phenylbenzoyl leucine

The resultant compound from Example 115D is hydrolyzed according to the procedure of Example 1B to give the title product.

Example 116

A-NH-SO₂-CH₂-B

The procedure of Example 115 is used with the exception that (2-phenyl-4-bromobenzoyl)-leucine methyl ester is replaced by a bromide from Table 2, entries 28-132 (B-Br) and (S)-5-aminomethyl-2-pyrrolidone is replaced by an amine from Table 3 (A-NH₂). For products derived from amines 146-206 from Table 3, the final LiOH hydrolysis step also hydrolyzes the ester on the fragment of the final compound that is derived from amines 146-206.



5905

Example 1174-(2-Thiazolyl)-2-phenylbenzoyl methionineExample 117A2-Thiazole boronic acid

5910 A solution of thiazole (1.0 equivalent) is lithiated with a slight excess of n-butyl lithium in THF (1.05 equivalents) and then treated with trimethyl borate (1.05 equivalents). The reaction mixture is quenched by the addition of aqueous HCl and the resulting boronate ester is cleaved by the addition of excess aqueous NaOH. After acidification and extraction into ethyl acetate the crude boronic acid is used without further purification.

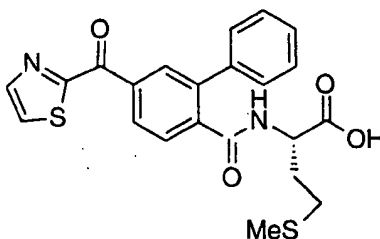
5915

Example 117B4-(2-Thiazolyl)-2-phenylbenzoyl methionine methyl ester

5920 A mixture of 4-bromo-2-phenylbenzoic acid methyl ester (1.0 equivalent), 2-thiazole boronic acid (1.0 equivalent) and catalytic Pd(PPh₃)₄ is heated in a two phase system of toluene and aqueous Na₂CO₃. After cooling, the resulting biaryl compound is isolated by evaporation of the organic phase and is purified by chromatography on silica gel.

Example 117C4-(2-Thiazolyl)-2-phenylbenzoyl methionine

5925 The resultant compound from Example 117C is hydrolyzed according to the procedure of Example 1B to give the title product.



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Example 1184-(2-Thiazolylcarbonyl)-2-phenylbenzoyl methionine

Example 118A4-(2-Thiazolylcarbonyl)-2-phenylbenzoyl methionine methyl ester

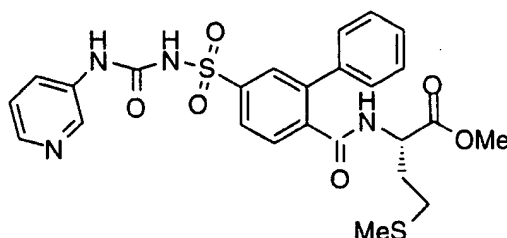
5935 A mixture of 4-bromo-2-phenylbenzoic acid methyl ester (1.0 equivalent), 2-thiazole boronic acid from Example 117A (1.0 equivalent) and catalytic $\text{Pd}(\text{PPh}_3)_4$ is heated in a two phase system of toluene and aqueous Na_2CO_3 previously purged with a large excess of carbon monoxide. The resulting diaryl ketone is isolated by evaporation of the organic phase and is purified by chromatography on silica gel.

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Example 118B4-(2-Thiazolylcarbonyl)-2-phenylbenzoyl methionine

The resultant compound from Example 118A is hydrolyzed according to the procedure of Example 1B to give the title product.

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Example 1194-[(3-Aminopyridyl)carbonylaminosulfonyl]-2-phenylbenzoylmethionine

5950

Example 119A4-Aminosulfonyl-2-phenylbenzoylmethionine methyl ester

5955 To a solution of 4-chlorosulfonyl-2-phenylbenzoyl methionine methyl ester from Example 5E in dichloromethane is added aqueous ammonia and the mixture is stirred until the reaction is judged complete by TLC analysis. The organic phase is separated, dried and evaporated and the product is purified by chromatography on silica gel.

Example 119B4-Isocyanatosulfonyl-2-phenylbenzoylmethionine methyl ester

5960 A mixture of the resultant sulfonamide from Example 119A in chlorobenzene is treated with oxalyl chloride according to the procedure of Franz et al. (*J. Org. Chem.*, 1964, 29, 2592) to give the title compound.

Example 119C

5965 4-[(A-aminopyridyl)carbonylaminosulfonyl]-2-phenylbenzoylmethionine methyl ester

A mixture of the resultant isocyanate from Example 119B (1 equivalent) in dichloromethane is treated with 3-aminopyridine (1 equivalent) and stirred until the reaction is judged complete by tlc analysis. The solvent is evaporated and the product is purified by chromatography on silica gel.

5970

Example 119D

4-[(A-aminopyridyl)carbonylaminosulfonyl]-2-phenylbenzoylmethionine

The resultant compound from Example 119C is hydrolyzed according to the procedure of Example 1B to give the title product.

5975

Example 120

A-NH-CO-NH-SO₂-B

5980 The anilines from Table 1 (B-NH₂) are reacted according to the procedures of Example 5E to afford the corresponding sulfonyl chlorides. These are reacted according to the procedure of Example 119 with the exception that 3-aminopyridine is replaced by an amine from Table 3 (A-NH₂). For products derived from amines 146-206 from Table 3, the final LiOH hydrolysis step also hydrolyzes the ester on the fragment of the final compound that is derived from amines 146-206.

5985 This example also encompasses compounds comprising a C-terminal ester moiety, in which case the final LiOH step is eliminated and the amino acid methyl esters used to prepare the anilines in Table 1 are replaced by the corresponding ethyl, propyl, isopropyl, butyl, sec-butyl, isobutyl, isoamyl, hexyl, octyl, cyclohexyl or phenethyl esters.

5990

Example 121

A-NH-CO-NH-SO₂-CH₂-B

5995 The bromides from Table 2, entries 28-132 (B-Br) are reacted according to the procedures of Example 115A-C to afford the corresponding sulfonyl chlorides. These are reacted according to the procedure of Example 119 with the exception that 3-aminopyridine is replaced by an amine from Table 3 (A-NH₂). For products derived from amines 146-206 from Table 3, the final LiOH hydrolysis step also hydrolyzes the ester on the fragment of the final compound that is derived from amines 146-206.

This example also encompasses compounds comprising a C-terminal ester moiety, in which case the final LiOH step is eliminated and the amino acid methyl esters used to prepare the

6000 bromides in Table 2 are replaced by the corresponding ethyl, propyl, isopropyl, butyl, sec-butyl, isobutyl, isoamyl, hexyl, octyl, cyclohexyl or phenethyl esters.

Example 122

A-O-CH₂-B

6005 The bromides from Table 2 (B-Br) are reacted according to the procedures of Example 16F-G. The resultant alcohols are reacted according to the procedure of Example 27 with the exception that 3-hydroxypyridine is replaced by an alcohol from Table 6 (A-OH). For products derived from alcohols 280-359 and 408-431 from Table 6, the LiOH hydrolysis step is followed by removal of the tert-butyloxycarbonyl (Boc) amine protecting group by
6010 stirring the resultant compound from the LiOH hydrolysis step in a 1:1 mixture of dichloromethane and trifluoroacetic acid until TLC analysis indicates that the reaction is complete. The solvent is evaporated and the residue is purified by chromatography on silica gel.

This example also encompasses compounds comprising a C-terminal ester moiety, in which
6015 case the final LiOH step is eliminated and the amino acid methyl esters used to prepare the bromides in Table 2 are replaced by the corresponding ethyl, propyl, isopropyl, butyl, sec-butyl, isobutyl, isoamyl, hexyl, octyl, cyclohexyl or phenethyl esters.

Example 123

A-O-CO-NH-B

6020 The procedure of Example 1 is used with the exception that 4-amino-2-phenylbenzoyl methionine methyl ester is replaced by an aniline from Table 1 (B-NH₂) and (S)-5-aminomethyl-2-pyrrolidone (1.0 equivalent) is replaced by an alcohol from Table 6 (A-OH, 1.0 equivalent) and CuCl (0.1 equivalent). For products derived from alcohols 280-359
6025 and 408-431 from Table 6, the LiOH hydrolysis step is followed by removal of the tert-butyloxycarbonyl (Boc) amine protecting group by stirring the resultant compound from the LiOH hydrolysis step in a 1:1 mixture of dichloromethane and trifluoroacetic acid until TLC analysis indicates that the reaction is complete. The solvent is evaporated and the residue is purified by chromatography on silica gel.

6030 This example also encompasses compounds comprising a C-terminal ester moiety, in which case the final LiOH step is eliminated and the amino acid methyl esters used to prepare the anilines in Table 1 are replaced by the corresponding ethyl, propyl, isopropyl, butyl, sec-butyl, isobutyl, isoamyl, hexyl, octyl, cyclohexyl or phenethyl esters.

Example 124

A-O-CS-NH-B

6035

The procedure of Example 1 is used with the exception that 4-amino-2-phenylbenzoyl methionine methyl ester is replaced by an aniline from Table 1 (B-NH₂), (S)-5-aminomethyl-2-pyrrolidone (1.0 equivalent) is replaced by an alcohol from Table 6 (A-OH, 1.0 equivalent) and CuCl (0.1 equivalent), and triphosgene (0.33 equivalent) is replaced by thiophosgene (1.0 equivalent). For products derived from alcohols 280-359 and 408-431 from Table 6, the LiOH hydrolysis step is followed by removal of the tert-butyloxycarbonyl (Boc) amine protecting group by stirring the resultant compound from the LiOH hydrolysis step in a 1:1 mixture of dichloromethane and trifluoroacetic acid until TLC analysis indicates that the reaction is complete. The solvent is evaporated and the residue is purified by chromatography on silica gel.

This example also encompasses compounds comprising a C-terminal ester moiety, in which case the final LiOH step is eliminated and the amino acid methyl esters used to prepare the anilines in Table 1 are replaced by the corresponding ethyl, propyl, isopropyl, butyl, sec-butyl, isobutyl, isoamyl, hexyl, octyl, cyclohexyl or phenethyl esters.

Example 125

A-O-SO-NH-B

The procedure of Example 3 is used with the exception that 4-amino-2-phenylbenzoyl methionine methyl ester is replaced by an aniline from Table 1 (B-NH₂) and (S)-5-aminomethyl-2-pyrrolidone (1.0 equivalent) is replaced by an alcohol from Table 6 (A-OH, 1.0 equivalent) and CuCl (0.1 equivalent). For products derived from alcohols 280-359 and 408-431 from Table 6, the LiOH hydrolysis step is followed by removal of the tert-butyloxycarbonyl (Boc) amine protecting group by stirring the resultant compound from the LiOH hydrolysis step in a 1:1 mixture of dichloromethane and trifluoroacetic acid until TLC analysis indicates that the reaction is complete. The solvent is evaporated and the residue is purified by chromatography on silica gel.

This example also encompasses compounds comprising a C-terminal ester moiety, in which case the final LiOH step is eliminated and the amino acid methyl esters used to prepare the anilines in Table 1 are replaced by the corresponding ethyl, propyl, isopropyl, butyl, sec-butyl, isobutyl, isoamyl, hexyl, octyl, cyclohexyl or phenethyl esters.

Example 126

A-O-SO₂-NH-B

The procedure of Example 4 is used with the exception that 4-amino-2-phenylbenzoyl methionine methyl ester is replaced by an aniline from Table 1 (B-NH₂) and (S)-5-aminomethyl-2-pyrrolidone (1.0 equivalent) is replaced by an alcohol from Table 6 (A-OH,

1.0 equivalent) and CuCl (0.1 equivalent). For products derived from alcohols 280-359 and 408-431 from Table 6, the LiOH hydrolysis step is followed by removal of the tert-butyloxycarbonyl (Boc) amine protecting group by stirring the resultant compound from the LiOH hydrolysis step in a 1:1 mixture of dichloromethane and trifluoroacetic acid until TLC analysis indicates that the reaction is complete. The solvent is evaporated and the residue is purified by chromatography on silica gel.

This example also encompasses compounds comprising a C-terminal ester moiety, in which case the final LiOH step is eliminated and the amino acid methyl esters used to prepare the anilines in Table 1 are replaced by the corresponding ethyl, propyl, isopropyl, butyl, sec-butyl, isobutyl, isoamyl, hexyl, octyl, cyclohexyl or phenethyl esters.

Example 127

A-O-CO-NH-CH₂-B

The bromides from Table 2 (B-Br) are reacted according to the procedures of Example 16F-G. The resultant alcohols are reacted according to the procedure of Example 18 with the exception that (*S*)-5-aminomethyl-2-pyrrolidone (1.0 equivalent) is replaced by an alcohol from Table 6 (A-OH, 1.0 equivalent) and CuCl (0.1 equivalent). For products derived from alcohols 280-359 and 408-431 from Table 6, the LiOH hydrolysis step is followed by removal of the tert-butyloxycarbonyl (Boc) amine protecting group by stirring the resultant compound from the LiOH hydrolysis step in a 1:1 mixture of dichloromethane and trifluoroacetic acid until TLC analysis indicates that the reaction is complete. The solvent is evaporated and the residue is purified by chromatography on silica gel.

This example also encompasses compounds comprising a C-terminal ester moiety, in which case the final LiOH step is eliminated and the amino acid methyl esters used to prepare the bromides in Table 2 are replaced by the corresponding ethyl, propyl, isopropyl, butyl, sec-butyl, isobutyl, isoamyl, hexyl, octyl, cyclohexyl or phenethyl esters.

Example 128

A-O-CS-NH-CH₂-B

The bromides from Table 2 (B-Br) are reacted according to the procedures of Example 16F-G. The resultant alcohols are reacted according to the procedure of Example 18 with the exception that (*S*)-5-aminomethyl-2-pyrrolidone (1.0 equivalent) is replaced by an alcohol from Table 6 (A-OH, 1.0 equivalent) and CuCl (0.1 equivalent), and triphosgene (0.33 equivalent) is replaced by thiophosgene (1.0 equivalent). For products derived from alcohols 280-359 and 408-431 from Table 6, the LiOH hydrolysis step is followed by

removal of the tert-butyloxycarbonyl (Boc) amine protecting group by stirring the resultant compound from the LiOH hydrolysis step in a 1:1 mixture of dichloromethane and trifluoroacetic acid until TLC analysis indicates that the reaction is complete. The solvent is evaporated and the residue is purified by chromatography on silica gel.

6115 This example also encompasses compounds comprising a C-terminal ester moiety, in which case the final LiOH step is eliminated and the amino acid methyl esters used to prepare the bromides in Table 2 are replaced by the corresponding ethyl, propyl, isopropyl, butyl, sec-butyl, isobutyl, isoamyl, hexyl, octyl, cyclohexyl or phenethyl esters.

6120

Example 129

A-O-SO-NH-CH₂-B

The bromides from Table 2 (B-Br) are reacted according to the procedures of Example 16F-G and 18A-B. The resultant amines are reacted according to the procedure of Example 3
6125 with the exception that (*S*)-5-aminomethyl-2-pyrrolidone (1.0 equivalent) is replaced by an alcohol from Table 6 (A-OH, 1.0 equivalent) and CuCl (0.1 equivalent). For products derived from alcohols 280-359 and 408-431 from Table 6, the LiOH hydrolysis step is followed by removal of the tert-butyloxycarbonyl (Boc) amine protecting group by stirring the resultant compound from the LiOH hydrolysis step in a 1:1 mixture of dichloromethane and trifluoroacetic acid until TLC analysis indicates that the reaction is complete. The
6130 solvent is evaporated and the residue is purified by chromatography on silica gel.

This example also encompasses compounds comprising a C-terminal ester moiety, in which case the final LiOH step is eliminated and the amino acid methyl esters used to prepare the bromides in Table 2 are replaced by the corresponding ethyl, propyl, isopropyl, butyl, sec-
6135 butyl, isobutyl, isoamyl, hexyl, octyl, cyclohexyl or phenethyl esters.

Example 130

A-O-SO₂-NH-CH₂-B

6140 The bromides from Table 2 (B-Br) are reacted according to the procedures of Example 16F-G and 18A-B. The resultant amines are reacted according to the procedure of Example 4 with the exception that (*S*)-5-aminomethyl-2-pyrrolidone (1.0 equivalent) is replaced by an alcohol from Table 6 (A-OH, 1.0 equivalent) and CuCl (0.1 equivalent). For products derived from alcohols 280-359 and 408-431 from Table 6, the LiOH hydrolysis step is
6145 followed by removal of the tert-butyloxycarbonyl (Boc) amine protecting group by stirring the resultant compound from the LiOH hydrolysis step in a 1:1 mixture of dichloromethane

and trifluoroacetic acid until TLC analysis indicates that the reaction is complete. The solvent is evaporated and the residue is purified by chromatography on silica gel. This example also encompasses compounds comprising a C-terminal ester moiety, in which case the final LiOH step is eliminated and the amino acid methyl esters used to prepare the bromides in Table 2 are replaced by the corresponding ethyl, propyl, isopropyl, butyl, sec-butyl, isobutyl, isoamyl, hexyl, octyl, cyclohexyl or phenethyl esters.

Example 131

A-S-B

The anilines from Table 1 (B-NH₂) are reacted according to the procedures of Example 13A. The resultant fluorides are reacted according to the procedure of Example 13 with the exception that 2-mercaptopyridine is replaced by a mercaptan from Table 7 (A-SH). For products derived from mercaptans 301-394 from Table 7, the LiOH hydrolysis step is followed by removal of the tert-butyloxycarbonyl (Boc) amine protecting group by stirring the resultant compound from the LiOH hydrolysis step in a 1:1 mixture of dichloromethane and trifluoroacetic acid until TLC analysis indicates that the reaction is complete. The solvent is evaporated and the residue is purified by chromatography on silica gel.

This example also encompasses compounds comprising a C-terminal ester moiety, in which case the final LiOH step is eliminated and the amino acid methyl esters used to prepare the anilines in Table 1 are replaced by the corresponding ethyl, propyl, isopropyl, butyl, sec-butyl, isobutyl, isoamyl, hexyl, octyl, cyclohexyl or phenethyl esters.

Example 132

A-S-CO-NH-B

The procedure of Example 1 is used with the exception that 4-amino-2-phenylbenzoyl methionine methyl ester is replaced by an aniline from Table 1 (B-NH₂) and (S)-5-aminomethyl-2-pyrrolidone (1.0 equivalent) is replaced by a mercaptan from Table 7 (A-SH). For products derived from mercaptans 301-394 from Table 7, the LiOH hydrolysis step is followed by removal of the tert-butyloxycarbonyl (Boc) amine protecting group by stirring the resultant compound from the LiOH hydrolysis step in a 1:1 mixture of dichloromethane and trifluoroacetic acid until TLC analysis indicates that the reaction is complete. The solvent is evaporated and the residue is purified by chromatography on silica gel.

This example also encompasses compounds comprising a C-terminal ester moiety, in which case the final LiOH step is eliminated and the amino acid methyl esters used to prepare the

anilines in Table 1 are replaced by the corresponding ethyl, propyl, isopropyl, butyl, sec-
6185 butyl, isobutyl, isoamyl, hexyl, octyl, cyclohexyl or phenethyl esters.

Example 133

A-S-CS-NH-B

6190 The procedure of Example 1 is used with the exception that 4-amino-2-phenylbenzoyl
methionine methyl ester is replaced by an aniline from Table 1 (B-NH₂), (S)-5-
aminomethyl-2-pyrrolidone (1.0 equivalent) is replaced by a mercaptan from Table 7 (A-
SH), and triphosgene (0.33 equivalent) is replaced by thiophosgene (1.0 equivalent). For
6195 products derived from mercaptans 301-394 from Table 7, the LiOH hydrolysis step is
followed by removal of the tert-butyloxycarbonyl (Boc) amine protecting group by stirring
the resultant compound from the LiOH hydrolysis step in a 1:1 mixture of dichloromethane
and trifluoroacetic acid until TLC analysis indicates that the reaction is complete. The
solvent is evaporated and the residue is purified by chromatography on silica gel.
This example also encompasses compounds comprising a C-terminal ester moiety, in which
6200 case the final LiOH step is eliminated and the amino acid methyl esters used to prepare the
anilines in Table 1 are replaced by the corresponding ethyl, propyl, isopropyl, butyl, sec-
butyl, isobutyl, isoamyl, hexyl, octyl, cyclohexyl or phenethyl esters.

Example 134

A-S-SO-NH-B

6205 The procedure of Example 3 is used with the exception that 4-amino-2-phenylbenzoyl
methionine methyl ester is replaced by an aniline from Table 1 (B-NH₂) and (S)-5-
aminomethyl-2-pyrrolidone (1.0 equivalent) is replaced by a mercaptan from Table 7 (A-
6210 SH). For products derived from mercaptans 301-394 from Table 7, the LiOH hydrolysis
step is followed by removal of the tert-butyloxycarbonyl (Boc) amine protecting group by
stirring the resultant compound from the LiOH hydrolysis step in a 1:1 mixture of
dichloromethane and trifluoroacetic acid until TLC analysis indicates that the reaction is
complete. The solvent is evaporated and the residue is purified by chromatography on silica
6215 gel.
This example also encompasses compounds comprising a C-terminal ester moiety, in which
case the final LiOH step is eliminated and the amino acid methyl esters used to prepare the
anilines in Table 1 are replaced by the corresponding ethyl, propyl, isopropyl, butyl, sec-
butyl, isobutyl, isoamyl, hexyl, octyl, cyclohexyl or phenethyl esters.

6220

Example 135A-S-SO₂-NH-B

The procedure of Example 4 is used with the exception that 4-amino-2-phenylbenzoyl methionine methyl ester is replaced by an aniline from Table 1 (B-NH₂) and (S)-5-aminomethyl-2-pyrrolidone (1.0 equivalent) is replaced by a mercaptan from Table 7 (A-SH). For products derived from mercaptans 301-394 from Table 7, the LiOH hydrolysis step is followed by removal of the tert-butyloxycarbonyl (Boc) amine protecting group by stirring the resultant compound from the LiOH hydrolysis step in a 1:1 mixture of dichloromethane and trifluoroacetic acid until TLC analysis indicates that the reaction is complete. The solvent is evaporated and the residue is purified by chromatography on silica gel.

This example also encompasses compounds comprising a C-terminal ester moiety, in which case the final LiOH step is eliminated and the amino acid methyl esters used to prepare the anilines in Table 1 are replaced by the corresponding ethyl, propyl, isopropyl, butyl, sec-butyl, isobutyl, isoamyl, hexyl, octyl, cyclohexyl or phenethyl esters.

Example 136A-S-CO-NH-CH₂-B

The bromides from Table 2 (B-Br) are reacted according to the procedures of Example 16F-G. The resultant alcohols are reacted according to the procedure of Example 18 with the exception that (S)-5-aminomethyl-2-pyrrolidone is replaced by a mercaptan from Table 7 (A-SH). For products derived from mercaptans 301-394 from Table 7, the LiOH hydrolysis step is followed by removal of the tert-butyloxycarbonyl (Boc) amine protecting group by stirring the resultant compound from the LiOH hydrolysis step in a 1:1 mixture of dichloromethane and trifluoroacetic acid until TLC analysis indicates that the reaction is complete. The solvent is evaporated and the residue is purified by chromatography on silica gel.

This example also encompasses compounds comprising a C-terminal ester moiety, in which case the final LiOH step is eliminated and the amino acid methyl esters used to prepare the bromides in Table 2 are replaced by the corresponding ethyl, propyl, isopropyl, butyl, sec-butyl, isobutyl, isoamyl, hexyl, octyl, cyclohexyl or phenethyl esters.

Example 137A-S-CS-NH-CH₂-B

The bromides from Table 2 (B-Br) are reacted according to the procedures of Example 16F-G. The resultant alcohols are reacted according to the procedure of Example 18 with the

exception that (*S*)-5-aminomethyl-2-pyrrolidone is replaced by a mercaptan from Table 7 (A-SH) and triphosgene (0.33 equivalent) is replaced by thiophosgene (1.0 equivalent).
6260 For products derived from mercaptans 301-394 from Table 7, the LiOH hydrolysis step is followed by removal of the tert-butyloxycarbonyl (Boc) amine protecting group by stirring the resultant compound from the LiOH hydrolysis step in a 1:1 mixture of dichloromethane and trifluoroacetic acid until TLC analysis indicates that the reaction is complete. The solvent is evaporated and the residue is purified by chromatography on silica gel.
6265 This example also encompasses compounds comprising a C-terminal ester moiety, in which case the final LiOH step is eliminated and the amino acid methyl esters used to prepare the bromides in Table 2 are replaced by the corresponding ethyl, propyl, isopropyl, butyl, sec-butyl, isobutyl, isoamyl, hexyl, octyl, cyclohexyl or phenethyl esters.

6270

Example 138

A-S-SO-NH-CH₂-B

The bromides from Table 2 (B-Br) are reacted according to the procedures of Example 16F-G and 18A-B. The resultant amines are reacted according to the procedure of Example 3
6275 with the exception that (*S*)-5-aminomethyl-2-pyrrolidone is replaced by a mercaptan from Table 7 (A-SH). For products derived from mercaptans 301-394 from Table 7, the LiOH hydrolysis step is followed by removal of the tert-butyloxycarbonyl (Boc) amine protecting group by stirring the resultant compound from the LiOH hydrolysis step in a 1:1 mixture of dichloromethane and trifluoroacetic acid until TLC analysis indicates that the reaction is
6280 complete. The solvent is evaporated and the residue is purified by chromatography on silica gel.

This example also encompasses compounds comprising a C-terminal ester moiety, in which case the final LiOH step is eliminated and the amino acid methyl esters used to prepare the bromides in Table 2 are replaced by the corresponding ethyl, propyl, isopropyl, butyl, sec-
6285 butyl, isobutyl, isoamyl, hexyl, octyl, cyclohexyl or phenethyl esters.

Example 139

A-S-SO₂-NH-CH₂-B

6290 The bromides from Table 2 (B-Br) are reacted according to the procedures of Example 16F-G and 18A-B. The resultant amines are reacted according to the procedure of Example 4 with the exception that (*S*)-5-aminomethyl-2-pyrrolidone is replaced by a mercaptan from Table 7 (A-SH). For products derived from mercaptans 301-394 from Table 7, the LiOH hydrolysis step is followed by removal of the tert-butyloxycarbonyl (Boc) amine protecting

6295 group by stirring the resultant compound from the LiOH hydrolysis step in a 1:1 mixture of dichloromethane and trifluoroacetic acid until TLC analysis indicates that the reaction is complete. The solvent is evaporated and the residue is purified by chromatography on silica gel.

This example also encompasses compounds comprising a C-terminal ester moiety, in which
6300 case the final LiOH step is eliminated and the amino acid methyl esters used to prepare the bromides in Table 2 are replaced by the corresponding ethyl, propyl, isopropyl, butyl, sec-butyl, isobutyl, isoamyl, hexyl, octyl, cyclohexyl or phenethyl esters.

6305 Example 140

A-O-B

The procedure of Example 6 is used with the exception that 4-amino-2-phenylbenzoyl methionine methyl ester is replaced by an aniline from Table 1 (B-NH₂) and 3-bromopyridine is replaced by a halide from Table 8 (A-Cl, A-Br, or A-I). For products
6310 derived from halides 202-239 from Table 8, the LiOH hydrolysis step is followed by removal of the tert-butyloxycarbonyl (Boc) amine protecting group by stirring the resultant compound from the LiOH hydrolysis step in a 1:1 mixture of dichloromethane and trifluoroacetic acid until TLC analysis indicates that the reaction is complete. The solvent is evaporated and the residue is purified by chromatography on silica gel.

6315 This example also encompasses compounds comprising a C-terminal ester moiety, in which case the final LiOH step is eliminated and the amino acid methyl esters used to prepare the anilines in Table 1 are replaced by the corresponding ethyl, propyl, isopropyl, butyl, sec-butyl, isobutyl, isoamyl, hexyl, octyl, cyclohexyl or phenethyl esters.

6320

Example 141

A-S-B

The procedure of Example 12 is used with the exception that 4-amino-2-phenylbenzoyl methionine methyl ester is replaced by an aniline from Table 1 (B-NH₂) and 2-chloromethylpyridine hydrochloride is replaced by a halide from Table 8 (A-Cl, A-Br, or A-I). For products derived from halides 202-239 from Table 8, the LiOH hydrolysis step is followed by removal of the tert-butyloxycarbonyl (Boc) amine protecting group by stirring the resultant compound from the LiOH hydrolysis step in a 1:1 mixture of dichloromethane and trifluoroacetic acid until TLC analysis indicates that the reaction is complete. The
6325 solvent is evaporated and the residue is purified by chromatography on silica gel.
6330

This example also encompasses compounds comprising a C-terminal ester moiety, in which case the final LiOH step is eliminated and the amino acid methyl esters used to prepare the anilines in Table 1 are replaced by the corresponding ethyl, propyl, isopropyl, butyl, sec-butyl, isobutyl, isoamyl, hexyl, octyl, cyclohexyl or phenethyl esters.

6335

Example 142

A-NH-B

The procedure of Example 24 is used with the exception that 4-amino-2-phenylbenzoyl methionine methyl ester is replaced by an aniline from Table 1 (B-NH₂) and 2-bromopyridine hydrobromide is replaced by a halide from Table 8 (A-Cl, A-Br, or A-I). For products derived from halides 202-239 from Table 8, the LiOH hydrolysis step is followed by removal of the tert-butyloxycarbonyl (Boc) amine protecting group by stirring the resultant compound from the LiOH hydrolysis step in a 1:1 mixture of dichloromethane and trifluoroacetic acid until TLC analysis indicates that the reaction is complete. The solvent is evaporated and the residue is purified by chromatography on silica gel.

6345

This example also encompasses compounds comprising a C-terminal ester moiety, in which case the final LiOH step is eliminated and the amino acid methyl esters used to prepare the anilines in Table 1 are replaced by the corresponding ethyl, propyl, isopropyl, butyl, sec-butyl, isobutyl, isoamyl, hexyl, octyl, cyclohexyl or phenethyl esters.

6350

Example 143

A-O-CH₂-B

The bromides from Table 2 (B-Br) are reacted according to the procedures of Example 16F-G. The resultant alcohols are reacted according to the procedure of Example 28 with the exception that 3-chloromethylpyridine hydrochloride is replaced by a halide from Table 8 (A-Cl, A-Br, or A-I). For products derived from halides 202-239 from Table 8, the LiOH hydrolysis step is followed by removal of the tert-butyloxycarbonyl (Boc) amine protecting group by stirring the resultant compound from the LiOH hydrolysis step in a 1:1 mixture of dichloromethane and trifluoroacetic acid until TLC analysis indicates that the reaction is complete. The solvent is evaporated and the residue is purified by chromatography on silica gel.

6360

This example also encompasses compounds comprising a C-terminal ester moiety, in which case the final LiOH step is eliminated and the amino acid methyl esters used to prepare the bromides in Table 2 are replaced by the corresponding ethyl, propyl, isopropyl, butyl, sec-butyl, isobutyl, isoamyl, hexyl, octyl, cyclohexyl or phenethyl esters.

6365

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Example 144A-S-CH₂-B

The bromides from Table 2 (B-Br) are reacted according to the procedures of Example 16F-G. The resultant alcohols are reacted according to the procedure of Example 37 with the exception that 2-bromothiazole is replaced by a halide from Table 8 (A-Cl, A-Br, or A-I).

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For products derived from halides 202-239 from Table 8, the LiOH hydrolysis step is followed by removal of the tert-butyloxycarbonyl (Boc) amine protecting group by stirring the resultant compound from the LiOH hydrolysis step in a 1:1 mixture of dichloromethane and trifluoroacetic acid until TLC analysis indicates that the reaction is complete. The solvent is evaporated and the residue is purified by chromatography on silica gel.

6380

This example also encompasses compounds comprising a C-terminal ester moiety, in which case the final LiOH step is eliminated and the amino acid methyl esters used to prepare the bromides in Table 2 are replaced by the corresponding ethyl, propyl, isopropyl, butyl, sec-butyl, isobutyl, isoamyl, hexyl, octyl, cyclohexyl or phenethyl esters.

6385

Example 145A-C≡C-B

The procedure of Example 47 is used with the exception that (2-phenyl-4-bromobenzoyl)-methionine methyl ester is replaced by a bromide from Table 2 (B-Br) and 4-

6390

bromoimidazole is replaced by a halide from Table 8 (A-Cl, A-Br, or A-I). For products derived from halides 202-239 from Table 8, the LiOH hydrolysis step is followed by removal of the tert-butyloxycarbonyl (Boc) amine protecting group by stirring the resultant compound from the LiOH hydrolysis step in a 1:1 mixture of dichloromethane and trifluoroacetic acid until TLC analysis indicates that the reaction is complete. The solvent is

6395

evaporated and the residue is purified by chromatography on silica gel. This example also encompasses compounds comprising a C-terminal ester moiety, in which case the final LiOH step is eliminated and the amino acid methyl esters used to prepare the bromides in Table 2 are replaced by the corresponding ethyl, propyl, isopropyl, butyl, sec-butyl, isobutyl, isoamyl, hexyl, octyl, cyclohexyl or phenethyl esters.

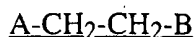
6400

Example 146A-CH=CH-B

The products from Example 145 are reacted according to the procedure of Example 48.

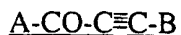
6405 This example also encompasses compounds comprising a C-terminal ester moiety, in which case the final LiOH step is eliminated and the amino acid methyl esters used to prepare the bromides in Table 2 are replaced by the corresponding ethyl, propyl, isopropyl, butyl, sec-butyl, isobutyl, isoamyl, hexyl, octyl, cyclohexyl or phenethyl esters.

6410

Example 147

The products from Example 146 are reacted according to the procedure of Example 49. This example also encompasses compounds comprising a C-terminal ester moiety, in which case the final LiOH step is eliminated and the amino acid methyl esters used to prepare the bromides in Table 2 are replaced by the corresponding ethyl, propyl, isopropyl, butyl, sec-butyl, isobutyl, isoamyl, hexyl, octyl, cyclohexyl or phenethyl esters.

6415

Example 148

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The bromides from Table 2 (B-Br) are reacted according to the procedure of Example 47A. The resultant acetylenes are reacted according to the procedure of Example 50 with the exception that 4-bromoimidazole is replaced by a halide from Table 8 (A-Cl, A-Br, or A-I). For products derived from halides 202-230 from Table 8, the LiOH hydrolysis step is followed by removal of the tert-butyloxycarbonyl (Boc) amine protecting group by stirring the resultant compound from the LiOH hydrolysis step in a 1:1 mixture of dichloromethane and trifluoroacetic acid until TLC analysis indicates that the reaction is complete. The solvent is evaporated and the residue is purified by chromatography on silica gel.

6425

This example also encompasses compounds comprising a C-terminal ester moiety, in which case the final LiOH step is eliminated and the amino acid methyl esters used to prepare the bromides in Table 2 are replaced by the corresponding ethyl, propyl, isopropyl, butyl, sec-butyl, isobutyl, isoamyl, hexyl, octyl, cyclohexyl or phenethyl esters.

6430

Example 149

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The products from Example 148 are reacted according to the procedure of Example 48.

This example also encompasses compounds comprising a C-terminal ester moiety, in which case the final LiOH step is eliminated and the amino acid methyl esters used to

6440 prepare the bromides in Table 2 are replaced by the corresponding ethyl, propyl, isopropyl, butyl, sec-butyl, isobutyl, isoamyl, hexyl, octyl, cyclohexyl or phenethyl esters.

Example 150

A-CO-CH₂-CH₂-B

6445 The products from Example 149 are reacted according to the procedure of Example 49.

This example also encompasses compounds comprising a C-terminal ester moiety, in which case the final LiOH step is eliminated and the amino acid methyl esters used to prepare the bromides in Table 2 are replaced by the corresponding ethyl, propyl, isopropyl, 6450 butyl, sec-butyl, isobutyl, isoamyl, hexyl, octyl, cyclohexyl or phenethyl esters.

Example 151

A-SO₂-B

The anilines from Table 1, entries 28-132 (B-NH₂) are reacted according to the 6455 procedures of Example 13A. The resultant fluorides are reacted according to the procedure of Example 13 with the exception that 2-mercaptopyridine is replaced by a mercaptan from Table 7 (A-SH). The resultant sulfides are oxidized according to the procedure of Example 14A. For products derived from mercaptans 301-394 from Table 7, the LiOH hydrolysis step is followed by removal of the tert-butyloxycarbonyl (Boc) amine protecting group by 6460 stirring the resultant compound from the LiOH hydrolysis step in a 1:1 mixture of dichloromethane and trifluoroacetic acid until TLC analysis indicates that the reaction is complete. The solvent is evaporated and the residue is purified by chromatography on silica gel.

This example also encompasses compounds comprising a C-terminal ester moiety, 6465 in which case the final LiOH step is eliminated and the amino acid methyl esters used to prepare the anilines in Table 1 are replaced by the corresponding ethyl, propyl, isopropyl, butyl, sec-butyl, isobutyl, isoamyl, hexyl, octyl, cyclohexyl or phenethyl esters.

Example 152

A-CH₂SO₂-B

6470 The procedure of Example 12 is used with the exception that 4-amino-2-phenylbenzoyl methionine methyl ester is replaced by an aniline from Table 1, entries 28-132 (B-NH₂) and 2-chloromethylpyridine hydrochloride is replaced by a halide from Table 8 (A-Cl, A-Br, or A-I). The resultant sulfides are oxidized according to the procedure of 6475 Example 14A. For products derived from halides 202-239 from Table 8, the LiOH hydrolysis step is followed by removal of the tert-butyloxycarbonyl (Boc) amine protecting

group by stirring the resultant compound from the LiOH hydrolysis step in a 1:1 mixture of dichloromethane and trifluoroacetic acid until TLC analysis indicates that the reaction is complete. The solvent is evaporated and the residue is purified by chromatography on silica gel.

This example also encompasses compounds comprising a C-terminal ester moiety, in which case the final LiOH step is eliminated and the amino acid methyl esters used to prepare the anilines in Table 1 are replaced by the corresponding ethyl, propyl, isopropyl, butyl, sec-butyl, isobutyl, isoamyl, hexyl, octyl, cyclohexyl or phenethyl esters.

Example 153

A-SO₂-CH₂-B

The bromides from Table 2, entries 28-132 (B-Br) are reacted according to the procedures of Example 16F-G. The resultant alcohols are reacted according to the procedure of Example 37 with the exception that 2-bromothiazole is replaced by a halide from Table 8 (A-Cl, A-Br, or A-I). The resultant sulfides are oxidized according to the procedure of Example 14A. For products derived from halides 202-239 from Table 8, the LiOH hydrolysis step is followed by removal of the tert-butyloxycarbonyl (Boc) amine protecting group by stirring the resultant compound from the LiOH hydrolysis step in a 1:1 mixture of dichloromethane and trifluoroacetic acid until TLC analysis indicates that the reaction is complete. The solvent is evaporated and the residue is purified by chromatography on silica gel.

This example also encompasses compounds comprising a C-terminal ester moiety, in which case the final LiOH step is eliminated and the amino acid methyl esters used to prepare the bromides in Table 2 are replaced by the corresponding ethyl, propyl, isopropyl, butyl, sec-butyl, isobutyl, isoamyl, hexyl, octyl, cyclohexyl or phenethyl esters.



Example 154

{4-[(3-sulfonylmethylpyridyl)amino]-2-phenylbenzoyl}methionine

Example 154A

{4-[(3-sulfonylmethylpyridyl)amino]-2-phenylbenzoyl}methionine methyl ester

6510 A mixture of 3-chlorosulfonylmethylpyridine hydrochloride (1.0 equivalent) and (4-amino-2-phenylbenzoyl)methionine methyl ester (1.0 equivalent) in dichloromethane is treated with triethylamine (2.2 equivalents). When judged complete by TLC analysis, the reaction is diluted with ethyl acetate, and then is washed with pH 4 water, saturated NaHCO₃, and brine. The mixture is dried and concentrated to give the crude title compound which is
6515 purified by chromatography on silica gel.

Example 154B

{4-[(3-sulfonylmethylpyridyl)amino]-2-phenylbenzoyl}methionine

The resultant compound from Example 154A is hydrolyzed according to the procedure of
6520 Example 1B to give the title product.

Example 155

A-CH₂SO₂-NH-B

The procedure of Example 154 is used with the exception that 4-amino-2-phenylbenzoyl
6525 methionine methyl ester is replaced by an aniline from Table 1 (B-NH₂) and 3-chlorosulfonylmethylpyridine hydrochloride is replaced by a sulfonyl chloride from Table 9 (A-SO₂Cl).

This example also encompasses compounds comprising a C-terminal ester moiety, in which case the final LiOH step is eliminated and the amino acid methyl esters used to prepare the
6530 anilines in Table 1 are replaced by the corresponding ethyl, propyl, isopropyl, butyl, sec-butyl, isobutyl, isoamyl, hexyl, octyl, cyclohexyl or phenethyl esters.

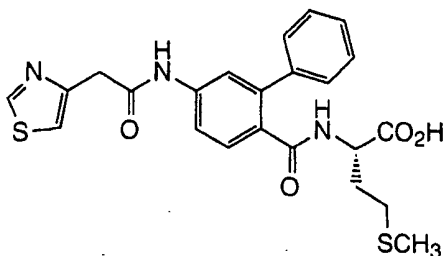
Example 156

A-SO₂-NH-CH₂-B

6535 The bromides from Table 2 (B-Br) are reacted according to the procedures of Example 16F-G. The resultant alcohols are converted to the corresponding amines according to the procedures of Examples 18A-B. These amines are reacted according to the procedure of Example 154 with the exception that -chlorosulfonylmethylpyridine hydrochloride is replaced by a sulfonyl chloride from Table 9 (A-SO₂Cl).

6540 This example also encompasses compounds comprising a C-terminal ester moiety, in which case the final LiOH step is eliminated and the amino acid methyl esters used to prepare the bromides in Table 2 are replaced by the corresponding ethyl, propyl, isopropyl, butyl, sec-butyl, isobutyl, isoamyl, hexyl, octyl, cyclohexyl or phenethyl esters.

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Example 162[4-(thiazo-4-ylmethylcarbonyl)amino-2-phenylbenzoyl]methionine

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Example 162AThioformamide

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To a mechanically-stirred solution of formamide (4.0 mL, 100 mmol) in THF (45 mL) was added P₄S₁₀ (4.5 g, 10.1 mmol) while the reaction mixture was maintained at <37 °C using an ice-water bath. The reaction mixture was then stirred for 5.5 hours at ambient temperature. The reaction mixture was filtered through a pad of celite and the filter cake was washed with THF. The filtrate was concentrated in vacuo and then under high vacuum for 4 hours to give thioformamide which was used without further purification.

Example 162B

6560

Ethyl 4-bromoacetoacetate

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To a mechanically-stirred solution of ethyl acetoacetate (59 mL, 463 mmol) in ether (75 mL) was added bromine (23.5 mL, 912 mmol) while the reaction temperature was maintained below 23 °C using an ice-water bath. The yellow-orange solution was stirred for 5 hours with cooling and then was stirred overnight at ambient temperature. Ice (60 g) was added and the reaction mixture was extracted with ether. The organic phase was washed twice with aqueous NaHCO₃ saturated with NaCl and once with brine. The ether solution was stirred for 1 day over CaCl₂ and then was filtered through celite. The filter cake was rinsed with dichloromethane. The filtrate was concentrated in vacuo to give ethyl 4-bromoacetoacetate (71.5 g) which was stored in the dark and stabilized with BaCO₃ (300 mg).

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Example 162CEthyl 4-Thiazolylacetate

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To a solution in absolute ethanol (18 mL) of ethyl 4-bromoacetoacetate (7.0 mL, 10.4 g, 49.7 mmol), prepared as in Example 162B, was added a solution in absolute ethanol/dioxane/toluene of thioformamide (4 g, 65 mmol), prepared as in Example 162A,

while the reaction temperature was maintained below 35 °C using an ice-water bath. The reaction mixture was stirred at reflux for 30 minutes, and then was cooled to ambient temperature. The reaction mixture was poured into aqueous 2N HCl (210 mL) and extracted twice with ether. The organic extracts were discarded and the aqueous phase was taken to pH 7-8 with NaHCO₃. The aqueous phase was extracted twice with ether. The ether extracts were dried over Na₂SO₄, filtered, and concentrated in vacuo to give 4.7 g of a dark oil. The oil was distilled at 20 mm Hg to give ethyl 4-thiazolylacetate (2.5 g, bp 111-122 °C) as light-yellow oil.

Example 162D

4-Thiazolylacetic acid

A mixture of ethyl 4-thiazolylacetate (2.4 g, 14 mmol), prepared as in Example 162C, and aqueous 10% NaOH was stirred for 10 minutes at ambient temperature. The reaction mixture was cooled to 0 °C and taken to pH 2-3 with concentrated HCl. The resulting white solid was filtered, washed with water and dried under high vacuum in the presence of P₂O₅ to give 4-thiazolylacetic acid (905 mg).

Example 162E

[4-(thiazo-4-ylmethylcarbonyl)amino-2-phenylbenzoyl]methionine methyl ester

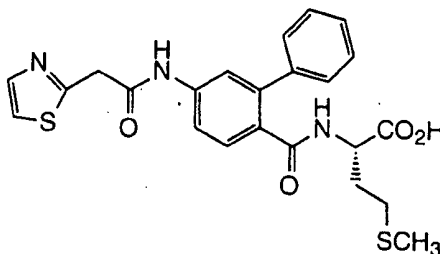
To a suspension in dichloromethane (10 mL) of 4-thiazolylacetic acid (460 mg, 3.22 mmol), prepared as in Example 162D was added oxalyl chloride (300 µL, 3.44 mmol) and DMF (5 mL). The mixture was stirred for 1.5 hours after bubbling ceased, and then was added over 5 minutes to a 5 °C 2-phase mixture of 4-amino-2-phenylbenzoyl methionine methyl ester (compound 8, 1.2 g, 3.2 mmol) in dichloromethane (12 mL) and saturated aqueous NaHCO₃ (15 mL). The cold bath was removed and the reaction mixture was stirred for 1.5 hours. The reaction mixture was partitioned between ethyl acetate and saturated aqueous NaHCO₃. The organic phase was dried over Na₂SO₄, filtered, and concentrated in vacuo to give a dark-brown residue (1.0 g). Chromatography on silica gel (10% ethyl acetate hexane) gave [4-(thiazo-4-ylmethylcarbonyl)amino-2-phenylbenzoyl]methionine methyl ester (581 mg) as a light-yellow powder.

Example 162F

[4-(thiazo-4-ylmethylcarbonyl)amino-2-phenylbenzoyl]methionine

The desired compound was prepared by saponification of [4-(thiazo-4-ylmethylcarbonyl)amino-2-phenylbenzoyl]methionine methyl ester, prepared as in Example 162E, using lithium hydroxide hydrate according to the method of Example 159. ¹H NMR (300 MHz, DMSO-d₆) δ 10.42 (s, 1H), 9.06 (d, 1H), 8.43 (d, 1H), 7.70 (d, 1H), 7.63

6615 (dd, 1H), 7.52 (d, 1H), 7.40 (d, 1H), 7.35 (m, 5H), 4.28 (m, 1H), 3.90 (s, 2H), 2.25 (m, 2H), 2.00 (s, 3H), 1.86 (m, 2H); MS (DCI-NH₃) m/e 470 (M+H)⁺. Anal calcd for C₂₃H₂₃N₃O₄S₂: C, 58.83; H, 4.94; N, 8.95. Found: C, 58.44; H, 4.87; N, 8.58.



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Example 163[4-(thiazol-2-yl)methylcarbonyl]amino-2-phenylbenzoyl]methionineExample 163A3-bromosuccinaldehydic acid ethyl ester

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To a 0-5 °C mechanically-stirred solution in diethyl ether (100 mL) of succinaldehydic acid ethyl ester (10.0 g, 77 mmol) was added bromine (3.9 g, 151 mmol) over 2.5 hours. The reaction mixture was stirred for an additional 1.25 hours and the ether was distilled at atmospheric pressure. The remaining yellow oil was distilled (6.0-6.5 mm Hg, bp 95-101 °C) to give 3-bromosuccinaldehydic acid ethyl ester (10.7 g, 66%).

6630

Example 163BEthyl 2-thiazolyl acetate

6635

To a slurry of thioformamide (3.9 g, 64 mmol) in diethyl ether (40 mL) and tetrahydrofuran (15 mL) was added 3-bromo-succinaldehydic acid ethyl ester (10.6 g, 51 mmol), prepared as in Example 163A. The reaction mixture was heated at reflux for 30 minutes, then ethanol (50 mL) was added, 30-40 mL of ether was distilled off, and the reaction mixture was heated at reflux for one hour. The reaction mixture was cooled to ambient temperature and aqueous 2N HCl (200 mL) was added. The mixture was extracted twice with ether. The aqueous phase was taken to pH 7-8 with NaHCO₃ (40 g) and was extracted with ether and twice with ethyl acetate. The combined organic layers were dried over Na₂SO₄, filtered, and concentrated in vacuo to give an orange oil which was purified by distillation (3 mm Hg, bp 109-111 °C) to give ethyl 2-thiazolyl acetate (2.15 g).

6640

Example 163C2-Thiazolyl acetic acid

6645

Ethyl 2-thiazolyl acetate (2.35 g, 13.7 mmol), prepared as in Example 163B, was added to 10% aqueous KOH. After about 10 minutes all of the oil dissolved to give a clear, bright-yellow solution. The reaction mixture was cooled to 0 °C and the pH was adjusted to 2-3 using concentrated HCl. The resulting solids were filtered off, rinsed with water, and dried over P₂O₅ under high vacuum to give 2-thiazolyl acetic acid (1.44 g).

Example 163D

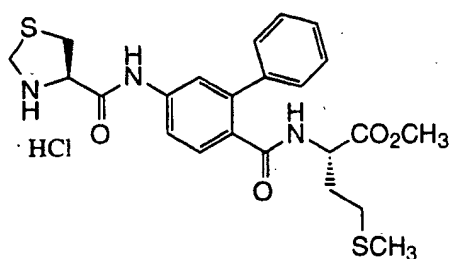
[4-(thiazol-2-ylmethylcarbonyl)amino-2-phenylbenzoyl]methionine methyl ester

To a solution in DMF (4 mL) of 2-thiazolyl acetic acid (300 mg, 2.1 mmol), prepared as in Example 163C, was added 3-hydroxy-1,2,3-benzotriazin-4(3H)-one (373 mg, 2.3 mmol) followed by ethyl dimethylaminopropyl carbodiimide hydrochloride (442 mg, 2.3 mmol), and a solution of 4-amino-2-phenylbenzoyl methionine methyl ester (compound 8, 760 mg, 2.0 mmol) in dichloromethane (3 mL) and the reaction mixture was stirred overnight at ambient temperature. The reaction mixture was diluted with ethyl acetate and washed saturated aqueous NaHCO₃ (2x) and brine. The organic phase was dried over Na₂SO₄, filtered, and concentrated in vacuo to give a brown solid (1.12 g). Chromatography on silica gel (ethyl acetate) gave [4-(thiazol-2-ylmethylcarbonyl)amino-2-phenylbenzoyl]methionine methyl ester (600 mg).

Example 163E

[4-(thiazol-2-ylmethylcarbonyl)amino-2-phenylbenzoyl]methionine

The desired compound was prepared by saponification of [4-(thiazol-2-ylmethylcarbonyl)amino-2-phenylbenzoyl]methionine methyl ester, prepared as in Example 163D) using the procedure of Example 159. ¹H NMR (300 MHz, DMSO-d₆) δ 10.50 (s, 1H), 9.00 (d, 1H), 8.45 (d, 1H), 7.79 (d, 1H), 7.67 (d, 1H), 7.61 (dd, 1H), 7.42 (d, 1H), 7.38 (m, 5H), 4.28 (m, 1H), 4.01 (s, 2H), 2.25 (m, 2H), 2.00 (s, 3H), 1.86 (m, 2H); MS (DCI-NH₃) m/e 470 (M+H)⁺. Anal calcd for C₂₃H₂₃N₃O₄S₂·H₂O: C, 56.66; H, 5.17; N, 8.62. Found: C, 56.75; H, 4.96; N, 8.45.

Example 164[4-((R)-thiazolidin-4-ylcarbonyl)amino-2-phenylbenzoyl]methionine methyl ester hydrochloride

6680

Example 164A*N*-tert-butoxycarbonyl-(R)-(-)-thiazolidine-4-carboxylic acid

To a solution of (R)-(-)-thiazolidine-4-carboxylic acid (1.0 g, 7.5 mmol) in aqueous 1N NaOH (9 mL) and THF (9 mL) was added a solution of di-*tert*-butyldicarbonate (1.62 g, 7.4 mmol) in THF (9 mL). An additional 2 mL of aqueous NaOH was added and the reaction mixture was stirred overnight at ambient temperature. Additional aqueous NaOH was added to make a clear solution and the reaction mixture was washed with hexanes (3x). The hexane extracts were washed twice with saturated aqueous NaHCO₃. The combined aqueous layers were acidified to pH 2 with 1.1 M NaHSO₄ and extracted twice with ether. The combined ether layers were dried over Na₂SO₄, filtered, and concentrated in vacuo to give *N*-tert-butoxycarbonyl-(R)-(-)-thiazolidine-4-carboxylic acid (1.3 g) which was used without further purification.

6690

Example 164B[4-(*N*-tert-butoxycarbonyl)-(R)-thiazolidin-4-ylcarbonyl)amino-2-phenylbenzoyl]methionine methyl ester

6695

The desired compound was prepared by coupling of *N*-tert-butoxycarbonyl-(R)-(-)-thiazolidine-4-carboxylic acid, prepared as in Example 164A with [4-amino-2-phenylbenzoyl]methionine methyl ester (compound 8) according to the method of Example 163D.

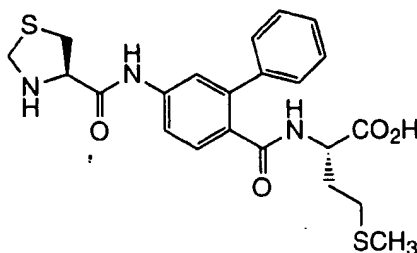
6700

Example 164C[4-((R)-thiazolidin-4-ylcarbonyl)amino-2-phenylbenzoyl]methionine methyl ester hydrochloride

6705

To a mixture of [4-(*N*-tert-butoxycarbonyl-(R)-thiazolidin-4-ylcarbonyl)amino-2-phenylbenzoyl]methionine methyl ester (270 mg, 0.47 mmol) and thiophenol (0.1 mL, 0.97 mmol) was added 4N HCl-dioxane (10 mL) and the reaction mixture was stirred for 45

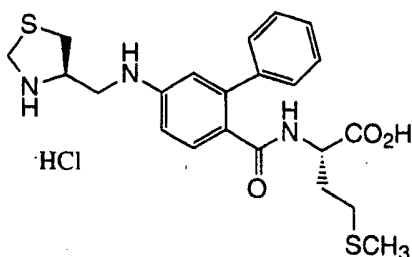
minutes at ambient temperature. The reaction mixture was partitioned between water and ether. The aqueous phase was extracted with ether. The organic extracts were discarded and the aqueous phase was lyophilized to give [4-((R)-thiazolidin-4-ylcarbonyl)amino-2-phenylbenzoyl]methionine methyl ester hydrochloride (150 mg). ¹H NMR (300 MHz, DMSO-d₆) δ 10.53 (s, 1H), 8.45 (d, 1H), 7.68 (m, 2H), 7.42 (dd, 1H), 7.37 (m, 5H), 4.27 (m, 4H), 3.70, 3.25, 3.12 (all m, total 3H), 2.24 (m, 2H), 2.00 (s, 3H), 1.85 (m, 2H); MS (APCI) m/e 474 (M+H)⁺. Anal calcd for C₂₃H₂₈ClN₃O₄S₂·1.4H₂O: C, 51.61; H, 5.80; N, 7.85. Found: C, 51.67; H, 5.55; N, 7.28.



Example 165

[4-((R)-thiazolidin-4-ylcarbonyl)amino-2-phenylbenzoyl]methionine

To a 0 °C solution in methanol (4.3 mL) of [4-((R)-thiazolidin-4-ylcarbonyl)amino-2-phenylbenzoyl]methionine methyl ester hydrochloride (75 mg, 0.15 mmol) was added a solution of lithium hydroxide hydrate (18 mg, 0.43 mmol) in water (0.5 mL). The reaction mixture was stirred for 1.5 hours, then the cold bath was removed and stirring was continued overnight at ambient temperature. The reaction mixture was concentrated in vacuo and aqueous 2N HCl was added to the residue. The cloudy solution was extracted with ethyl acetate and chloroform-isopropanol. The combined organic extracts were washed with brine, dried over Na₂SO₄, filtered, and concentrated in vacuo to give 4-((R)-thiazolidine-4-carbonyl)amino-2-phenylbenzoyl]methionine (67 mg). ¹H NMR (300 MHz, DMSO-d₆) δ 11.10 (s, 1H), 8.60 (d, 1H), 7.70 (s, 1H), 7.68 (dd, 1H), 7.44 (dd, 1H), 7.37 (m, 5H), 4.63 (m, 1H), 4.37 (m, 3H), 3.70 (m, 1H), 3.63 (s, 3H), 3.40 (m, 1H), 2.24 (m, 2H), 2.00 (s, 3H), 1.85 (m, 2H); MS (APCI) m/e 460 (M+H)⁺. Anal calcd for C₂₂H₂₅N₃O₄S₂·0.8 HCl: C, 54.06; H, 5.32; N, 8.60. Found: C, 54.21; H, 5.34; N, 8.00.

Example 166[4-((R)-thiazolidin-4-ylmethyl)amino-2-phenylbenzoyl]methionine hydrochloride

6740

Example 166A*N*-tert-butoxycarbonyl-(R)-(-)thiazolidine-4-carboxylic acid-*N*-methoxy-*N*-methyl amide

To a solution in DMF (10 mL) of *N*-tert-butoxycarbonyl-(R)-(-)thiazolidine-4-carboxylic acid (777 mg, 3.33 mmol), prepared as in Example 164A, 3-hydroxy-1,2,3-benzotriazin-4(3H)-one (602 mg, 3.69 mmol), and ethyl dimethylaminopropyl carbodiimide hydrochloride (709 mg, 3.70 mmol) was added *N*,*O*-dimethylhydroxylamine hydrochloride (357 mg, 3.66 mmol) and 4-methylmorpholine (0.44 mL, 4.01 mmol) and the reaction mixture was stirred overnight at ambient temperature. The reaction mixture was diluted with ethyl acetate and extracted with aqueous 1M H₃PO₄ (2x), saturated aqueous NaHCO₃ (2x), and brine. The organic phase was dried over Na₂SO₄, filtered, and concentrated in vacuo. Chromatography on silica gel (2:1 hexane-ethyl acetate) gave *N*-tert-butoxycarbonyl-(R)-(-)thiazolidine-4-carboxylic acid-*N*-methoxy-*N*-methyl amide (605 mg) as a thick yellow oil.

6745

6750

Example 166B*N*-tert-butoxycarbonyl-(R)-(-)thiazolidine-4-carboxaldehyde

To a -78 °C solution in THF (6 mL) of *N*-tert-butoxycarbonyl-(R)-(-)thiazolidine-4-carboxylic acid-*N*-methoxy-*N*-methyl amide (550 mg, 2.0 mmol) was added lithium aluminum hydride (1.0 M in THF, 3.0 mL, 3.0 mmol) and the reaction mixture was stirred for 2.5 hours. The reaction was quenched with 10% aqueous citric acid (30 mL) and warmed to ambient temperature. The mixture was warmed to ambient temperature and extracted with ether (3x). The combined organic extracts were washed with brine, dried over MgSO₄, filtered, and concentrated in vacuo to give *N*-tert-butoxycarbonyl-(R)-(-)thiazolidine-4-carboxaldehyde (440 mg) which was used without further purification.

6755

6760

Example 166C

6765 [4-(*N*-*tert*-butoxycarbonyl)-(R)-thiazolidin-4-ylmethyl)amino-2-phenylbenzoyl]methionine methyl ester

N-*tert*-butoxycarbonyl-(R)-(-)-thiazolidine-4-carboxaldehyde was reductively aminated with 4-amino-2-phenylbenzoyl methionine methyl ester (compound 8) according to the procedure of Example 158B.

Example 166C

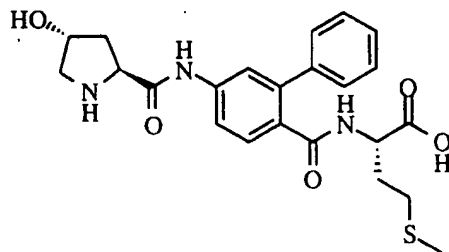
[4-((R)-thiazolidin-4-ylmethyl)amino-2-phenylbenzoyl]methionine methyl ester

The desired compound was prepared according to the method of Example 164C, except substituting [4-(*N*-*tert*-butoxycarbonyl-(R)-thiazolidin-4-ylmethyl)amino-2-phenylbenzoyl]methionine methyl ester, prepared as in Example 166B, for [4-(*N*-*tert*-butoxycarbonyl-(R)-thiazolidin-4-ylcarbonyl)amino-2-phenylbenzoyl]methionine methyl ester.

Example 166D

[4-((R)-thiazolidin-4-ylmethyl)amino-2-phenylbenzoyl]methionine hydrochloride

The desired compound was prepared by saponification of [4-((R)-thiazolidin-4-ylmethyl)amino-2-phenylbenzoyl]methionine methyl ester, prepared as in Example 166C according to the procedure of Example 165. ¹H NMR (300 MHz, DMSO-d₆) δ 8.03 (d, 1H), 7.33 (m, 6H), 6.69 (dd, 1H), 6.59 (d, 1H), 4.30 (dd, 2H), 4.23 (m, 1H), 3.86 (m, 1H), 3.46 (dd, 2H), 3.22 (dd, 1H), 2.91 (m, 1H), 2.24 (m, 2H), 2.00 (s, 3H), 1.85 (m, 2H); MS (APCI) m/e 446 (M+H)⁺, 444 (M-H)⁻. Anal calcd for C₂₂H₂₇N₃O₃S₂·HCl·0.25H₂O: C, 54.31; H, 5.90; N, 8.64. Found: C, 54.20; H, 6.07; N, 8.35.

Example 169

[4-(4-hydroxy-prolinyl)amino-2-phenylbenzoyl]methionine trifluoroacetate

Example 169A

N-Boc-4-(*t*-butyldimethylsilyl)hydroxyproline

To a solution of 1.3 g (3.6 mmol) of *N*-Boc-4-(*t*-butyldimethylsilyloxy)proline methyl ester, prepared as described by Rosen et al., *J. Med. Chem.* **1988**, *31*, 1598, in 10 ml of methanol was added 5 ml (5 mmol) of 1 N LiOH in an ice bath. The reaction mixture was stirred for 30 min. The reaction mixture was adjusted to pH 2-3 with 1 N HCl at the same temperature and the solvent was evaporated. The resulting residue was partitioned between dichloromethane and water, and extracted 3 times with dichloromethane. The combined organic solution was washed with 1 N HCl and water, dried over anhydrous magnesium sulfate, and concentrated in vacuo to give 1.05 g (96 %) of *N*-Boc-4-(*t*-butyldimethylsilyl-oxy)proline as a foamy solid which was used without further purification.

Example 169B[4-[*N*-Boc-4-(*t*-butyldimethylsilyloxy)prolinyl]amino-2-phenylbenzoyl]methionine methyl ester

To a solution in dichloromethane (15 mL) of *N*-Boc-4-(*t*-butyldimethylsilyloxy)proline (1.0 g, 3.29 mmol), prepared as in Example 169A, was added 550 μ l (3.9 mmol) of triethylamine in an ice bath under argon, followed by 470 μ l (3.6 mmol) of isobutyl chloroformate. The reaction mixture was stirred for 40 minutes. At this time TLC showed the absence of the starting material. To this solution, 1.07 g (2.97 mmol) of [2-phenyl-4-aminobenzoyl]methionine methyl ester (compound 8) in 10 ml of dichloromethane was introduced. The reaction mixture was stirred overnight, during which time the ice bath expired. The reaction mixture was washed with 1 N HCl, 5 % sodium bicarbonate, and water, dried over magnesium sulfate, and solvent was removed. The residue was flash-chromatographed on silica gel (7:3 hexanes-ethyl acetate) to yield 1.92 g (94 %) of {4-[*N*-Boc-4-(*t*-butyldimethylsilyl)hydroxyprolinyl]-2-phenylaminobenzoyl}methionine methyl ester as a foamy solid. mp 83 °C; $[\alpha]_D^{25}$ -36.2 (c =0.63, CHCl₃); ¹H NMR (300 MHz, CDCl₃) δ 9.94 (s, 1H), 7.53-7.26 (m, 8H), 6.41 (d, 1H, J =6.0 Hz), 4.55 (m, 4H), 3.63 (s, 3H), 3.57 (m, 1H), 3.32 (m, 1H), 2.30 (m, 1H), 2.05 (m, 2H), 1.94 (s, 3H), 1.83 (m, 1H), 1.73 (m, 1H), 1.45 (s, 9H), 0.86 (s, 9H), 0.05 (s, 6H); ¹³C NMR (CDCl₃) δ 171.8, 170.7, 169.3, 155.6, 140.0, 129.7, 129.0, 128.5, 128.2, 127.4, 120.2, 117.7, 80.7, 77.2, 70.1, 59.5, 54.7, 52.1, 51.7, 38.0, 30.9, 29.5, 28.2, 25.5, 17.7, 15.1, 4.9; HRMS (EI) calculated for C₃₅H₅₁N₃O₇SSi: 685.9498, found: 685.3217.

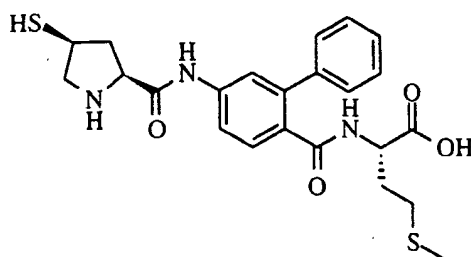
Example 169C[4-(*N*-Boc-4-hydroxyprolinyl)amino-2-phenylbenzoyl]methionine methyl ester

To a solution of 1.82 g (2.65 mmol) of {4-[*N*-Boc-4-(*t*-butyldimethylsilyloxy)-prolinyl]amino-2-phenylbenzoyl}methionine methyl ester, prepared as in Example 169B, in 20 ml of THF was added 3 ml (3 mmol) of 1 M tetra-*n*-butylammonium fluoride in THF. The reaction mixture was stirred overnight, diluted with ethyl acetate, and washed 3 times with water. The combined aqueous washings were extracted 3 times with ethyl acetate. The combined organic fractions were dried over magnesium sulfate and concentrated in vacuo. The crude product was purified by flash chromatography on silica gel (ethyl acetate) to obtain 864 mg (57 %) of [4-(*N*-Boc-4-hydroxyprolinyl)amino-2-phenylbenzoyl]methionine methyl ester as a white solid: mp 121-123 °C; $[\alpha]_D^{25}$ -53.3 ($c=0.43$, CHCl₃); ¹H NMR (300 MHz, CDCl₃) δ 9.84 (s, 1H), 7.60-7.38 (m, 8H), 6.35 (br s, 1H), 4.58-4.51 (br s, 4H), 3.64 (s, 3H), 3.57 (m, 1H), 3.48 (m, 1H), 2.63 (m, 1H), 2.44 (br s, 1H), 2.07 (m, 2H), 1.98 (s, 3H), 1.86 (m, 1H), 1.72 (m, 1H), 1.44 (s, 9H); HRMS (EI) calculated for C₂₉H₃₇N₃O₇S: 571.6872, found: 571.2352.

Example 169D

[4-(4-hydroxyprolinyl)amino-2-phenylbenzoyl]methionine trifluoroacetate

To a solution of 358 mg (0.62 mmol) of [4-(*N*-Boc-4-hydroxyprolinyl)amino-2-phenylbenzoyl]methionine methyl ester, prepared as in Example 169C, in 6 ml of methanol was added 1 ml (1 mmol) of 1 N LiOH in an ice bath and the reaction mixture was stirred for 4 hours. The reaction mixture was adjusted to pH 2-3 with 1 N HCl at the same temperature and the solvent was evaporated. The resulting residue was partitioned between chloroform and water and extracted 3 times with chloroform. The combined organic solution was washed with 1 N HCl and water, dried over anhydrous magnesium sulfate, and concentrated in vacuo to give 317 mg (92 %) of [4-(4-hydroxyprolinyl)amino-2-phenylbenzoyl]methionine as a white solid. To a 5 ml of 1:1 solution of TFA and dichloromethane was added 306 mg (0.54 mmol) of the acid. After 3 hours, the reaction mixture was thoroughly evaporated under high vacuum to give an oily residue. The residue was triturated with anhydrous ether and the white solid was collected by filtration to give 254 mg (72%) of [4-(4-hydroxyprolinyl)amino-2-phenylbenzoyl]methionine trifluoroacetate: HPLC 90 % (purity); mp 127 (sub.), 154-157 °C (dec.); ¹H NMR (300 MHz, CDCl₃ + CD₃OD) δ 7.53-7.29 (m, 8H), 4.67 (m, 1H), 4.58 (s, 1H), 4.50 (m, 1H), 2.57 (m, 1H), 2.14 (m, 2H), 2.01 (s, 3H), 1.96 (m, 1H), 1.76 (m, 1H); ¹³C NMR (CD₃OD) δ 174.8, 172.6, 168.1, 142.4, 141.2, 140.6, 133.2, 130.0, 129.6, 129.5, 128.8, 122.2, 119.3, 71.2, 60.6, 55.2, 52.9, 39.9, 31.4, 30.9, 15.0.



Example 170

6870

[4-((2S,4S)-4-mercaptopyrrolidin-2-carboxy)amino-2-phenylbenzoyl]methionine trifluoroacetate

Example 170A

6875

[4-((2S,4S)-1-Boc-4-acetylthiopyrrolidin-2-carboxy)amino-2-phenylbenzoyl]methionine methyl ester

6880

To a solution of 140 mg (0.22 mmol) of {4-[*N*-Boc-4-(*t*-butyldimethylsilyloxy)-prolinyl]amino-2-phenylbenzoyl}methionine methyl ester, prepared as in Example 169C, in 10 ml of THF was added 128 mg (0.48 mmol) of triphenylphosphine, followed by 96 μ l (0.49 mmol) of diisopropyl azodicarboxylate at 0 °C under argon atmosphere. The reaction mixture was stirred for 40 minutes and 35 μ l (0.49 mmol) of thiolacetic acid was added to this mixture at the same temperature. The reaction mixture was stirred overnight, during which time the ice bath expired. The solvent was removed, and a 3:1 solution of hexanes and ethyl acetate was introduced to the resulting residue to precipitate the insoluble by-products. After removal of by-products, the solution was concentrated. The crude product was chromatographed on silica gel (3:1 hexanes-ethyl acetate) to yield 123 mg (89 %)

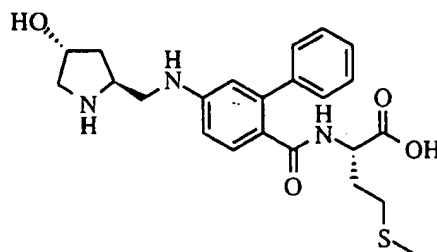
6885 of [4-((2S,4S)-1-Boc-4-acetylthiopyrrolidin-2-carboxy)amino-s-phenylbenzoyl]methionine methyl ester as a foamy solid: mp 97 °C; $[\alpha]^{25}_D$ -105.2 ($c=0.27$, CHCl₃); ¹H NMR (300 MHz, CDCl₃) δ 9.87 (s, 1H), 7.68-7.38 (m, 8H), 6.37 (s, 1H), 4.58 (br s, 4H), 4.02 (m, 1H), 3.64 (s, 3H), 3.33 (br s, 1H), 2.52 (br s, 1H), 2.30 (s, 3H), 2.03 (t, 2H, $J=7.8$ Hz), 1.99 (s, 3H), 1.90 (m, 1H), 1.74 (m, 1H), 1.45 (s, 9H); ¹³C NMR (CDCl₃) δ 195.5, 172.2, 169.9, 169.3, 169.0, 155.3, 140.3, 140.0, 130.2, 129.2, 128.7, 128.4, 127.7, 120.6, 117.9, 81.6, 60.2, 53.2, 52.3, 51.9, 39.3, 34.0, 31.2, 30.5, 29.6, 28.3, 15.2; MS (EI) m/z (relative intensity) 629 (M^+ , 6), 571 (25), 529 (45), 196 (100).

6895

Example 170B

[4-((2S,4S)-4-mercaptopyrrolidin-2-carboxy)amino-2-phenylbenzoyl]methionine trifluoroacetate

To a solution of 120 mg (0.19 mmol) of [4-((2S,4S)-1-Boc-4-acetylthiopyrrolidin-2-carboxy)amino-2-phenylbenzoyl]methionine methyl ester, prepared as in Example 170A, in 5 ml of THF was added 1 ml (1 mmol) of 1 N LiOH in an ice bath. The reaction mixture was stirred for 2 hours. The reaction mixture was adjusted to pH 2-3 with 1 N HCl at the same temperature and the solvent was evaporated. The residue was partitioned between dichloromethane and water and extracted 3 times with dichloromethane. The combined organic solution was washed with 1 N HCl and water, dried over anhydrous magnesium sulfate, and concentrated in vacuo to give 105 mg (94 %) of [4-((2S,4S)-4-thiopyrrolidin-2-carboxy)amino-2-phenylbenzoyl]methionine as a white solid. To 5 ml of a 1:1 solution of TFA and dichloromethane were added 105 mg (0.17 mmol) of the acid, followed by a few drops of triethylsilane. After 30 minutes, the reaction mixture was thoroughly evaporated in high vacuum to give an oily residue. The residue was triturated with anhydrous ether and the white solid was collected by filtration to give 90 mg (80%) of [4-((2S,4S)-4-thiopyrrolidin-2-carboxy)amino-2-phenylbenzoyl]methionine trifluoroacetate: HPLC 86 % (purity); mp 169 °C (dec.); ¹H NMR (300 MHz, CD₃OD) δ 7.59-7.28 (m, 8H), 4.39 (m, 2H), 3.53 (m, 1H), 3.38 (m, 1H), 3.22-3.12 (m, 2H), 2.87 (m, 1H), 2.12 (m, 1H), 2.00-1.92 (m, 5H), 1.72 (m, 1H); ¹³C NMR (CD₃OD) δ 175.0, 172.7, 167.5, 142.6, 140.7, 133.4, 130.2, 129.8, 129.7, 129.0, 122.5, 119.5, 61.8, 55.3, 53.2, 41.1, 36.2, 31.6, 31.1, 15.3.



Example 171

[4-((2S,4R)-4-hydroxypyrrolidin-2-ylmethyl)amino-2-phenylbenzoyl]methionine hydrochloride

Example 171A

(2S,4R)-1-Boc-4-[(t-butyldimethylsilyloxy]-2-(hydroxymethyl)pyrrolidine

A suspension of calcium chloride (780 mg, 7 mmol) and 530 mg (14 mmol) of sodium borohydride in 25 ml of THF was stirred at ambient temperature for 5 hours. To this suspension was added 2.5 g (7 mmol) of (2S,4R)-1-Boc-4-[(t-butyldimethylsilyloxy]-2-(carbomethoxy)pyrrolidine methyl ester in 5 ml of THF and the reaction mixture was stirred overnight. Excess hydride was destroyed by adding hydrated sodium sulfate. The white

precipitate was removed by suction filtration through a pad of Celite, and the filtrate was dried over magnesium sulfate and concentrated to give 2.25 g (97 %) of (2S,4R)-1-Boc-4-[(*t*-butyldimethylsilyloxy)-2-(hydroxymethyl)pyrrolidine as a colorless oil: ¹H NMR (CDCl₃) δ 0.05 (s, 6H), 0.85 (s, 9H), 1.47 (s, 9H), 1.90 (m, 1H), 3.27-4.25 (complex m, 7H), 4.89 (br d, 1H, *J*=6.6 Hz); MS (EI) *m/z* 332 (*M*⁺), 258.

Example 171B

(2S,4R)-1-Boc-4-[*t*-butyldimethylsilyloxy]pyrrolidin-2-aldehyde

To a solution of 1 ml (14.1 mmol) of DMSO in 7 ml of dichloromethane were added 1.48 ml (10.4 mmol) of trifluoroacetic anhydride in 3.5 ml of dichloromethane at -78 °C under a slight stream of argon. After 10 min, 2.35 g (7 mmol) of (2S,4R)-1-Boc-4-[*t*-butyldimethylsilyloxy]-2-(hydroxymethyl)pyrrolidine, prepared as in Example 171A, in 7 ml of dichloromethane was added to this mixture at the same temperature. The reaction mixture was stirred for 1 hour. To this solution was added 3 ml (21.5 mmol) of triethylamine. The reaction mixture was stirred for 1 hour at -78 °C, slowly warmed to room temperature, and concentrated. The residue was chromatographed on silica gel (9:1 hexanes-ethyl acetate to yield 1.08 g (47 %) of (2S,4R)-1-Boc-4-[*t*-butyldimethylsilyloxy]-pyrrolidin-2-aldehyde as an oil: ¹H NMR (300 MHz, CDCl₃) δ 9.39 (s, 1H), 4.33 (m, 1H), 4.17 (m, 1H), 3.48 (m, 1H), 3.35 (m, 1H), 1.93 (m, 2H), 1.41 (s, 9H), 0.82 (s, 9H), 0.07 (s, 6H).

Example 171C

{4-[(2S,4R)-1-Boc-4-*t*-butyldimethylsilyloxy]pyrrolidin-2-ylmethyl}amino-2-phenylbenzoyl}methionine methyl ester

To a solution of 0.75 g (2.09 mmol) of [2-phenyl-4-aminobenzoyl]methionine methyl ester (compound 8) and 0.7 g (2.1 mmol) of (2S,4R)-1-Boc-4-[*t*-butyldimethylsilyloxy]-pyrrolidin-2-aldehyde, prepared as in Example 171B, in 10 ml of methanol were added 1 ml of acetic acid, followed by 0.2 g (3.1 mmol) of sodium cyanoborohydride. The reaction mixture was stirred overnight. After removal of the solvent, the residue was partitioned with ethyl acetate and 5 % sodium bicarbonate, and extracted 3 times with ethyl acetate. The combined organic solution was washed with water and brine, dried over magnesium sulfate, and solvent was removed. The residue was flash-chromatographed on silica gel (2:1 hexanes-ethyl acetate) to yield 261 mg (74 %) of {4-[(2S,4R)-1-Boc-4-(*t*-butyldimethylsilyloxy)pyrrolidin-2-ylmethyl]amino-2-phenylbenzoyl}methionine methyl ester as a white solid: mp 48 °C; [α]_D²⁵ -15.6 (*c*=1.03, CHCl₃); ¹H NMR (300 MHz, CDCl₃) δ 7.67 (d, 1H, *J*=8.5 Hz), 7.37 (m, 6H), 6.57 (1, 1H), 6.37 (s, 1H), 5.60 (br s, 2H), 4.60 (m, 1H), 4.31 (m, 2H), 3.77 (s, 3H), 3.61-3.10 (m, 5H), 2.06 (t, 2H, *J*=8.2 Hz), 1.98 (s, 3H), 1.85 (m, 1H), 1.60 (m, 1H), 1.43 (s, 9H);

0.84 (s, 9H), 0.03 (s, 6H); HRMS (EI) calculated for C₃₅H₅₃N₃O₆SSi: 671.3424, found: 671.3424.

6970

Example 171D

[4-((2S,4R)-N-Boc-4-hydroxy)pyrrolidin-2-ylmethyl)amino-2-phenylbenzoyl]methionine methyl ester

To a solution of 770 mg (1.14 mmol) of {4-[(2S,4R)-1-Boc-4-(*t*-butyldimethylsilyloxy)-pyrrolidin-2-ylmethyl]amino-2-phenylbenzoyl}methionine methyl ester, prepared as in Example 171C, in 10 ml of THF was added 2 ml (2 mmol) of 1 M tetra-*n*-butylammonium fluoride in THF. The reaction mixture was stirred for 15 minutes at ambient temperature, diluted with ethyl acetate, and washed 3 times with water. The combined aqueous washings were extracted 3 times with ethyl acetate. The combined organic fractions were dried over magnesium sulfate and concentrated in vacuo. The crude product was purified by flash chromatography on silica gel (ethyl acetate) to obtain 467 mg (73 %) of 2-[4-((2S,4R)-N-Boc-4-hydroxypyrrolidin-2-ylmethyl)amino-2-phenylbenzoyl]methionine methyl ester as a foamy solid: mp 81 °C; [α]_D²⁴ -15.9 (*c*=0.74, CHCl₃); ¹H NMR (300 MHz, CDCl₃) δ 7.63 (d, 1H, *J*=9.0 Hz), 7.35 (m, 6H), 6.57 (br s, 1H), 6.38 (br s, 1H), 5.67 (d, 1H, *J*=7.6 Hz), 5.54 (br s, 1H), 4.55 (m, 1H), 4.09 (m, 2H), 3.59 (s, 3H), 3.37-3.16 (m, 5H), 2.71 (br s, 1H), 2.04 (m, 2H), 1.96 (s, 3H), 1.80 (m, 1H), 1.60 (m, 1H), 1.40 (s, 9H); ¹³C NMR (CDCl₃) δ 172.0, 168.5, 156.4, 150.0, 141.7, 141.1, 131.3, 128.6, 127.7, 121.8, 113.5, 110.8, 80.2, 69.5, 69.1, 60.3, 55.3, 54.8, 52.2, 51.7, 49.0, 38.6, 31.5, 29.4, 28.3, 25.5, 15.2; HRMS (EI) calculated for C₂₉H₃₉N₃O₆S: 557.2559, found: 557.2559.

6990

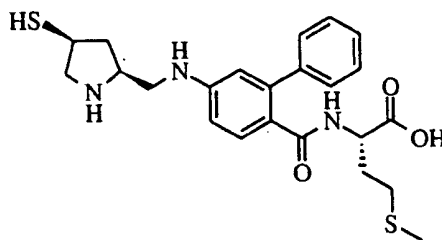
Example 171E

[4-((2S,4R)-N-Boc-4-hydroxypyrrolidin-2-ylmethyl)amino-2-phenylbenzoyl]methionine hydrochloride

To a solution of 125mg (0.22 mmol) of [4-((2S,4R)-N-Boc-4-hydroxypyrrolidin-2-ylmethyl)amino-2-phenylbenzoyl]methionine methyl ester, prepared as in Example 171D, in 5 ml of THF was added 0.5 ml (0.5 mmol) of 1 N LiOH in an ice bath. The reaction mixture was stirred for 5 hours. The reaction mixture was adjusted to pH 2-3 with 1 N HCl at the same temperature and the solvent was evaporated. The residue was partitioned with dichloromethane and water, and extracted 3 times with dichloromethane. The combined organic solution was washed with 1 N HCl and water, dried over anhydrous magnesium sulfate, and concentrated in vacuo to give 50 mg (42 %) of the resulting free acid as a solid. To a 2 ml of 1:1 solution of TFA and dichloromethane was added 50 mg (0.09 mmol) of the acid. After 30 minutes, the reaction mixture was thoroughly evaporated in high vacuum to

7000

7005 give an oily residue. The residue was triturated with 0.3 ml of 3 M anhydrous HCl-ether in
 5 ml of ether and the white solid was collected by filtration to give 35 mg (74 %) of [4-
 ((2S,4R)-N-Boc-4-hydroxypyrrolidin-2-ylmethyl)amino-2-phenylbenzoyl]methionine
 hydrochloride: HPLC 72 % (purity). ¹H NMR (300 MHz, CD₃OD) δ 7.71-7.30 (m, 6H),
 6.76 (dd, 1H, J= 8.4, 2.4 Hz), 6.69 (d, 1H, J= 2.2 Hz), 4.55 (d, 1H, J= 4.0 Hz), 4.44
 7010 (dd, 1H, J= 9.3, 4.2 Hz), 4.12 (m, 1H), 3.62-3.19 (m, 4H), 2.02 (s, 3H), 2.21-1.75 (m,
 6H).



7015 Example 172
[4-((2S,4S)-4-thiopyrrolidin-2-yl-methylamino)-2-phenylbenzoyl]methionine hydrochloride

Example 172A
[4-((2S,4S)-N-Boc-4-acetylthiopyrrolidin-2-yl-methylamino)-2-phenylbenzoyl]methionine
 7020 methyl ester and
[4-((2S,5S)-4-Boc-1,4-diazabicyclo(2,2,1)octan-1-yl)-2-phenylbenzoyl]methionine methyl
ester

To a solution of 153 mg (0.27 mmol) of 2-Phenyl-4-[(2S,4R)-N-Boc-4-
 hydroxy]pyrrolidine-2-methyl]aminobenzoyl]methionine methyl ester, prepared as in
 7025 Example 171D, in 10 ml of THF were added 142 mg (0.54 mmol) of triphenylphosphine,
 followed by 107 μ l (0.54 mmol) of diisopropyl azodicarboxylate at 0 °C under argon
 atmosphere. The mixture was stirred for 30 minutes and 40 μ l (0.56 mmol) of thiolacetic
 acid was added at the same temperature. The reaction mixture was stirred overnight, during
 which time the ice bath expired. The solvent was removed, and a 3:1 solution of hexanes
 7030 and ethyl acetate was introduced to the residue to precipitate the insoluble by-products. After
 removal of by-products, the solution was concentrated. The crude products were
 chromatographed on silica gel (1:1 hexanes-ethyl acetate) to give 106 mg (63 %) of [4-
 ((2S,4S)-N-Boc-4-acetylthiopyrrolidin-2-yl-methylamino)-2-phenylbenzoyl]methionine
 methyl ester and 35 mg (24 %) of the bicyclic [4-((2S,5S)-4-Boc-1,4-
 7035 diazabicyclo(2,2,1)octan-1-yl)-2-phenylbenzoyl]methionine methyl ester as white solids.

[4-((2S,4S)-N-Boc-4-acetylthiopyrrolidin-2-yl-methylamino)-2-phenylbenzoyl]methionine methyl ester: ^1H NMR (300 MHz, CDCl_3) δ 7.65 (d, 1H, $J=8.4$ Hz), 7.37 (m, 6H), 6.60 (br s, 1H), 6.41 (br s, 1H), 5.66 (d, 1H, $J=7.8$ Hz), 5.53 (br s, 1H), 4.58 (m, 1H), 4.23 (br s, 1H), 4.02 (br s, 1H), 3.87 (m, 1H), 3.60 (s, 3H), 3.38-3.12 (br s, 2H), 3.12 (dd, 1H, $J=6.7, 11.4$ Hz), 2.52 (m, 1H), 2.30 (s, 3H), 2.05 (t, 2H, $J=7.6$ Hz), 1.97 (s, 3H), 1.82 (m, 1H), 1.62 (m, 1H), 1.41 (s, 9H); ^{13}C NMR (CDCl_3) δ 195.0, 172.1, 168.5, 155.8, 150.0, 141.8, 141.4, 131.5, 128.8, 128.6, 127.8, 122.2, 113.7, 111.0, 80.7, 60.4, 56.5, 52.3, 51.8, 49.2, 39.3, 36.0, 31.7, 30.6, 29.6, 28.4, 15.3; HRMS (EI) calculated for $\text{C}_{31}\text{H}_{41}\text{N}_3\text{O}_6\text{S}_2$: 615.2436, found: 615.2436.

[4-((2S,5S)-4-Boc-1,4-diazabicyclo(2,2,1)octan-1-yl)-2-phenylbenzoyl]methionine methyl ester: ^1H NMR (300 MHz, CDCl_3) δ 7.75 (d, 1H, $J=8.6$ Hz), 7.54-7.40 (m, 6H), 6.57 (d, 1H, $J=9.0$ Hz), 6.36 (s, 1H), 5.68 (br s, 1H), 4.63 (m, 2H), 4.42 (br s, 1H), 3.63 (s, 3H), 3.58-3.17 (m, 5H), 2.10 (m, 2H), 1.98 (s, 3H), 1.86 (m, 1H), 1.66 (m, 1H), 1.41 (s, 9H); ^{13}C NMR (CDCl_3) δ 172.2, 168.5, 154.2, 148.7, 142.0, 141.4, 132.1, 131.7, 129.0, 128.8, 128.1, 122.1, 113.7, 111.2, 80.0, 57.4, 56.4, 52.5, 52.0, 37.9, 37.4, 31.9, 29.7, 28.7, 15.5; HRMS (EI) calculated for $\text{C}_{29}\text{H}_{37}\text{N}_3\text{O}_5\text{S}$: 539.2454, found: 539.2453.

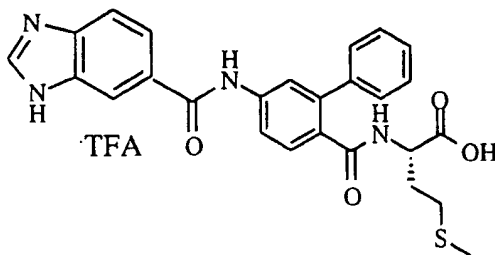
Example 172B

[4-((2S,4S)-4-thiopyrrolidin-2-yl-methylamino)-2-phenylbenzoyl]methionine hydrochloride

To a solution of 86 mg (0.14 mmol) of [4-((2S,4S)-N-Boc-4-acetylthiopyrrolidin-2-yl-methylamino)-2-phenylbenzoyl]methionine methyl ester in 2 ml of THF was added 0.4 ml (0.4 mmol) of 1 N LiOH in an ice bath. The reaction mixture was stirred for 2 hours. The reaction mixture was adjusted to pH 2-3 with 1 N HCl at the same temperature and the solvent was evaporated. The resulting residue was partitioned between dichloromethane and water, and extracted 3 times with dichloromethane. The combined organic solution was washed with 1 N HCl and water, dried over anhydrous magnesium sulfate, and concentrated in vacuo to give 67 mg (85 %) of the resulting free acid as a white solid. To 2 ml of 1:1 solution of TFA and dichloromethane were added 67 mg (0.12 mmol) of the acid, followed by a few drops of triethylsilane. After 30 minutes, The reaction mixture was thoroughly evaporated under high vacuum to give an oily residue. The residue was triturated with anhydrous ether and the white solid was collected by filtration to give 62 mg (97 %) of [4-((2S,4S)-4-thiopyrrolidin-2-yl-methylamino)-2-phenylbenzoyl]methionine hydrochloride: HPLC 83% (purity); ^1H NMR (300 MHz, CD_3OD) δ 7.46-7.35 (m, 6H), 6.76 (d, 1H, $J=8.4$ Hz), 6.70 (s, 1H), 4.45 (m, 1H), 3.91 (m, 1H), 3.68-3.30 (m, 5H), 3.15 (m, 1H), 2.66 (m, 1H), 2.20 (m, 1H), 2.10 (m, 1H), 2.01 (s, 3H), 1.79 (m, 2H); ^{13}C NMR

(CD₃OD) δ 175.0, 173.3, 150.5, 143.5, 142.3, 131.3, 129.9, 129.6, 128.7, 125.9, 115.9, 112.5, 60.9, 54.6, 53.3, 45.8, 40.3, 35.4, 31.8, 31.0, 15.3.

7075



Example 182

[4-(1H-benzimidazol-5-ylcarboxyamino)-2-phenylbenzoyl]methionine trifluoroacetate

7080

Example 182A

(1H-1-*p*-Toluenesulfonylbenzimidazol-5-yl)carboxylic acid

5-Benzimidazolecarboxylic acid (1.0 g, 6.2 mmol) and *p*-toluenesulfonyl chloride (1.2 g, 6.2 mmol) were suspended in 10 mL of distilled water. Aqueous 1N sodium hydroxide was added periodically to maintain a pH of approximately 9 over a period of 4 hours. The reaction mixture was washed with methylene chloride (3X50 mL.) and was adjusted to pH 3 with 1N hydrochloric acid. The precipitate which formed was collected by vacuum filtration, washed with distilled water and hexanes and air dried to give (1H-1-*p*-toluenesulfonylbenzimidazol-5-yl)carboxylic acid (0.75 g, 38%) as a white solid.

7090

Example 182B

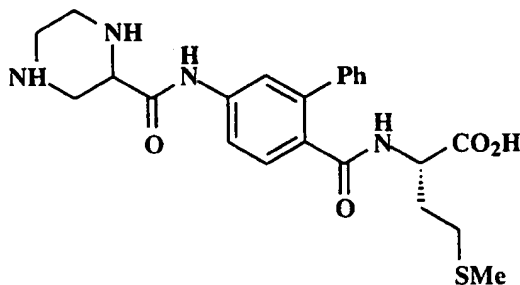
[4-(1H-1-*p*-Toluenesulfonylbenzimidazol-5-ylcarboxyamino)-2-phenylbenzoyl]methionine methyl ester

To 50 mL of methylene chloride containing [4-amino-2-phenylbenzoyl]methionine methyl ester hydrochloride (compound 8, 0.65 g, 1.64 mmol) and 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (EDCI, 0.34 g, 1.8 mmol) was added (1H-1-*p*-toluenesulfonylbenzimidazol-5-yl)carboxylic acid (0.52 g, 1.64 mmol), prepared as in Example 182A, and the mixture was cooled to 0°C. Triethylamine (0.16 g, 1.64 mmol) was slowly added to the stirred solution. After 1 hour, the ice bath was removed and the reaction was stirred for an additional 96 hours. The organic layer was washed with distilled water, dried over magnesium sulfate and concentrated. The residue was purified by flash column chromatography (4:1 ethyl acetate/hexanes) to give [4-(1H-1-*p*-toluenesulfonylbenzimidazol-5-ylcarboxyamino)-2-phenylbenzoyl]methionine methyl ester (0.63 g, 59%) as a white solid.

Example 182C

[4-(1H-benzimidazol-5-ylcarboxyamino)-2-phenylbenzoyl]methionine trifluoroacetate

[4-(1H-1-*p*-Toluenesulfonylbenzimidazol-5-ylcarboxyamino)-2-phenylbenzoyl]methionine methyl ester (0.2 g, 0.3 mmol), prepared as in Example 182B, was added to 5 mL of tetrahydrofuran (THF) and the mixture was cooled to 0°C. Lithium hydroxide (5 mL, 0.5M) was slowly added and the reaction mixture was stirred for 2 hours. The THF was removed by evaporation and 0.5M HCl was added to adjust the pH to between 2 and 3 and the precipitate which formed was collected by vacuum filtration. The solid was purified by reverse phase preparative HPLC (Waters 25X10 cm, C-18 column, 220 nm UV detector, flow rate 15 mL/min, linear gradient from 5% acetonitrile and 95% water containing 0.1% TFA to 60% acetonitrile in 40 minutes) and pure fractions were pooled and lyophilized to give [4-(1H-benzimidazol-5-ylcarboxyamino)-2-phenylbenzoyl]methionine trifluoroacetate as a white solid (0.146 g, 87%). ¹H NMR (300 MHz, DMSO-d₆) δ 10.56 (s, 1H), 9.05 (s, 1H), 8.47 (d, 1H, *J* = 7.8 Hz), 8.40 (s, 1H), 8.04 (d, 1H, *J* = 8.1 Hz), 7.88-7.89 (m, 2H), 7.33-7.48 (m, 6H), 4.30 (m, 1H), 2.16-2.29 (m, 2H), 2.06 (s, 3H), 1.84-2.00 (m, 2H). MS *m/e* 489 (M+H)⁺.



Example 185

[4-(piperidin-2-ylcarboxyamino)-2-phenylbenzoyl]methionine hydrochloride.

Example 185A

di-*tert*-butoxycarbonylpiperidine-2-carboxylic acid

Di-*tert*-butyl dicarbonate (15.5 g, 70.2 mmol) was added to a solution of piperazine-2-carboxylic acid (4.85 g, 23.4 mmol) and NaOH (98 mL of a 1 M aqueous solution, 98 mmol) in THF (100 mL). The cloudy mixture was stirred for 16 hours and then concentrated under reduced pressure to remove THF. The residue was saturated with solid NaHCO₃ and extracted with ether (2 x 30 mL). The aqueous layer was cooled to 0 °C and then adjusted to pH = 3 with 2 M aqueous HCl. A precipitate developed. The mixture was

7135 extracted with CH₂Cl₂ (3 x 75 mL), and the organic extracts were dried over MgSO₄,
filtered, and concentrated under reduced pressure to provide 7.61 g (98%) of di-*tert*-
butoxycarbonylpiperidine-2-carboxylic acid as a tan solid. ¹H NMR (CDCl₃) δ 1.45 (s, 18
H), 2.80-2.98 (br, 1 H), 3.04-3.36 (br comp, 2 H), 3.70-3.83 (br, 1 H), 3.94-4.05 (br, 1
H), 4.44-4.65 (br comp, 2 H), 4.80-4.95 (br, 1 H). LRMS (CI): 292, 331 (M+1)⁺, 348
7140 (M+NH₄)⁺.

Example 185B

[4-(di-*tert*-butoxycarbonylpiperidin-2-ylcarboxyamino)-2-phenylbenzoyl]methionine methyl
ester.

7145 The desired compound was prepared by coupling di-*tert*-butoxycarbonylpiperidine-2-
carboxylic acid with [4-amino-2-phenylbenzoyl]methionine methyl ester (compound 8)
according to the procedure of Example 184A.

Example 185C

7150 [4-(di-*tert*-butoxycarbonylpiperidin-2-ylcarboxyamino)-2-phenylbenzoyl]methionine.

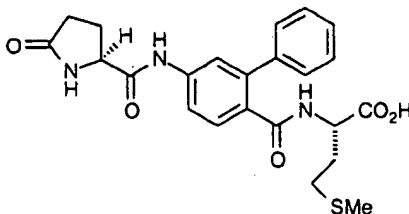
Lithium hydroxide hydrate (0.411 g, 9.60 mmol) was added to a solution of [4-(di-*tert*-
butoxycarbonylpiperidin-2-yl)carboxyamino-2-phenylmethionine methyl ester (*ca* 0.8 g,
1.20 mmol), prepared in Example 185B, in THF/H₂O (4:1, 12 mL). The solution was
stirred for 20 hours and then treated with 1 M aqueous HCl (10 mL). The mixture was
7155 extracted with ethyl acetate (5 x 10 mL), and the organic extracts were rinsed with 1:1 brine/1
N HCl (10 mL), dried over Na₂SO₄, and concentrated under reduced pressure to provide [4-
(di-*tert*-butoxycarbonylpiperidin-2-yl)carboxyamino-2-phenylmethionine (0.72 g) as a white
foam (est. 89%). ¹H NMR (CD₃OD) δ 1.3-1.5 (br, 18 H), 1.7-1.9 (br comp, 2 H), 2.0
(br s, 3 H), 2.1-2.3 (br comp, 2 H), 2.9-4.8 (br comp, 8 H), 7.3-7.5 (br comp, 6 H), 7.5-
7160 7.6 (br m, 1 H), 7.6-7.7 (br m, 1 H). LRMS (CI): 657 (M+1)⁺, 457, 330.

Example 185D

[4-(piperidin-2-ylcarboxyamino)-2-phenylbenzoyl]methionine hydrochloride.

[4-(di-*tert*-butoxycarbonylpiperidin-2-ylcarboxyamino)-2-phenylbenzoyl]methionine
7165 (0.72 g, 1.07 mmol), prepared in Example 185C, was treated with HCl (9.6 mL of a 4 M
solution in dioxane, 38.5 mmol) and the solution was stirred for 5 minutes, at which time a
pink precipitate was observed. The mixture was treated with pentane (10 mL) and the
precipitate was isolated by filtration to afford [4-(piperidin-2-yl)carboxyamino-2-
phenylbenzoyl]methionine hydrochloride (0.448 g, 86%). ¹H NMR (CD₃OD) δ 1.73-1.88
7170 (m, 1 H), 1.93-2.05 (comp, 4 H), 2.05-2.14 (m, 1 H), 2.14-2.26 (m, 1 H), 3.32-3.64

(comp, 5 H), 3.68-3.85 (comp, 2 H), 3.97 (dd, 1 H), 4.13 (dd, 1 H), 4.73 (dd, 1 H), 7.35-7.50 (comp, 5 H), 7.51-7.59 (m, 1 H), 7.74-7.80 (m, 1 H). LRMS (CI): 457 (M+1)⁺.



Example 202

[4-(2-pyrrolidinone-5-ylcarbonylamino)-2-phenylbenzoyl]methionine

Example 202A

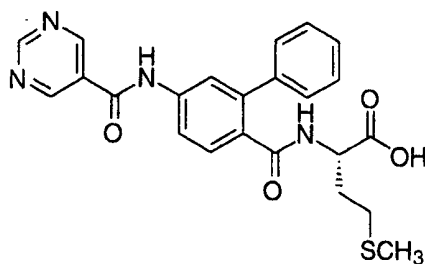
[4-(2-pyrrolidinone-5-ylcarbonylamino)-2-phenylbenzoyl]methionine methyl ester

To a solution of L-pyroglutamic acid (49mg, 0.38 mmol) in 5 mL of DMF was added 3-hydroxy-1,2,3-benzotriazin-4(3H)-one (62mg, 0.38 mmol), (3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (58mg, 0.30 mmol) and [4-amino-2-phenylbenzoyl-L-methionine methyl ester (90mg, 0.38 mmol), prepared as in Example 192B, and the reaction mixture was stirred at 25 °C for 12 hours. The reaction mixture was taken up in ethyl acetate and washed with 10 mL 1N HCl, 5 mL satd aqueous NaHCO₃ and brine (3 x 10 mL). The organic layer was dried over Na₂SO₄, filtered and evaporated. Purification by radial chromatography (2-5% methanol-ethyl acetate gradient) to give [4-(2-pyrrolidinone-5-ylcarbonylamino)-2-phenylbenzoyl]methionine methyl ester (92mg, 79%) as a white solid.

Example 202B

[4-(2-pyrrolidinone-5-ylcarbonylamino)-2-phenylbenzoyl]methionine

LiOH monohydrate (29mg, 0.69 mmol) was dissolved in 1 mL H₂O and added to a solution of [4-(2-pyrrolidinone-5-ylcarbonylamino)-2-phenylbenzoyl]methionine methyl ester, prepared as in Example 202A, (108mg, 0.23 mmol) in 3 mL of THF and the reaction mixture was stirred at 25 °C for 1 hour. The reaction mixture was evaporated and 2 mL of 1N HCl was added to the aqueous residue. The resulting precipitate was filtered and dried under vacuum to give [4-(2-pyrrolidinone-5-ylcarbonylamino)-2-phenylbenzoyl]methionine (96 mg, 91%). ¹H NMR (300 MHz, CD₃OD) δ 7.70 - 7.60 (m, 3H), 7.45 - 7.30 (m, 5H), 4.40 (bs, 1H), 2.60 - 2.10 (m, 7H), 2.00 (s, 3H), 1.90 - 1.80 (m, 2H). CIMS MH⁺ 456.

Example 219[4-(5-pyrimidylcarboxyamino)-2-phenylbenzoyl]methionine

7205

Example 219A5-pyrimidinecarboxylic acid methyl ester

A mixture of 5-bromopyrimidine (1.59 g, 10 mmol), 1-propanol (1.5 mL, 20 mmol), bis(triphenylphosphine)palladium(II) chloride (400 mg, 0.50 mmol) and tributylamine (3.72 g, 20 mmol) in DMF was stirred at 90 °C under a carbon monoxide balloon for 10 hours. The reaction mixture was diluted with ethyl acetate (100 mL), washed with potassium dihydrogenphosphate (1.0 M, 20 mL, twice), water, and brine, dried over anhydrous magnesium sulfate, filtered, and concentrated *in vacuo*. The residue was then purified by column chromatography (50:50:10 hexane-dichloromethane-ether) to give 3-pyrimidinecarboxylic acid methyl ester (715 mg, 52%). ¹H NMR (300 MHz, CDCl₃) δ 9.38 (s, 1H), 9.30 (s, 2H), 4.36 (t, 2H), 1.83 (sextet, 2H), 1.05 (t, 3H).

7210

7215

Example 219B[4-(5-pyrimidylcarboxyamino)-2-phenylbenzoyl]methionine methyl ester

A mixture of the 5-pyrimidinecarboxylic acid methyl ester prepared in Example 219A (682 mg, 4.94 mmol) and aqueous sodium hydroxide solution (4.0 M, 2.5 mL) in THF was heated at 60 °C for 1.5 hours. Hydrochloric acid (6.0 N, 2 mL) was added to the reaction mixture, and the solvent was evaporated *in vacuo*. The residue was dried under high vacuum at 50 °C for 1 hour, and the redissolved in THF. To the acid solution was added (4-amino-2-phenylbenzoyl)methionine methyl ester (compound 8, 1.97 g, 5.0 mmol), 3-hydroxy-1,2,3-benzotriazin-4(3H)-one (0.978 g, 6.0 mmol), 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide (1.15 g, 6.0 mmol) and triethylamine (2.8 mL, 20 mmol). After 14 hours, the reaction mixture was diluted with ethyl acetate (100 mL), washed with water and brine, dried over anhydrous magnesium sulfate, filtered, and concentrated *in vacuo*. The residue was then purified by column chromatography (50% ethyl acetate-hexane, then ethyl acetate) to give [4-(3-pyrimidylcarboxyamino)-2-phenylbenzoyl]methionine methyl ester (0.937 g, 41%). ¹H NMR (300 MHz, CDCl₃) δ 9.34 (s, 1H), 9.19 (s, 2H), 9.01 (s, 1H), 7.64 (d, 1H), 7.52 (d, 1H), 7.42 (dd, 1H), 7.33 (m, 5H), 6.20 (br d, 1H), 4.66 (m, 1H),

7220

7225

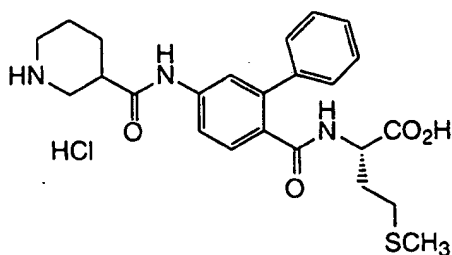
7230

3.69 (s, 3H), 2.14 (t, 2H), 2.02 (s, 3H), 1.95 (m, 1H), 1.78 (m, 1H). MS (CI⁺) m/e 465 (M+H)⁺.

Example 219C

[4-(5-pyrimidylcarboxyamino)-2-phenylbenzoyl]methionine

To a solution of the [4-(5-pyrimidylcarboxyamino)-2-phenylbenzoyl]methionine methyl ester prepared in Example 210B (324 mg, 0.70 mmol) in methanol (2 mL) was added aqueous sodium hydroxide (2.0 N, 1.0 mL). After 14 hours, the reaction mixture was diluted with ethyl acetate (100 mL), washed twice with potassium dihydrogenphosphate (1.0 M, 20 mL each), water and brine, dried over anhydrous sodium sulfate, filtered, and concentrated *in vacuo*. The residue was then purified by column chromatography (ethyl acetate, then 95:5:0.5 ethyl acetate-methanol-acetic acid) to give [4-(3-pyrimidylcarboxyamino)-2-phenylbenzoyl]methionine (265 mg, 84%). ¹H NMR (300 MHz, DMSO-d₆) δ 10.80 (s, 1H), 9.38 (s, 1H), 9.30 (s, 2H), 8.51 (d, 1H), 7.83 (m, 2H), 7.50 (d, 1H), 7.39 (m, 5H), 4.29 (m, 1H), 2.28 (m, 2H), 2.00 (s, 3H), 1.86 (m, 2H). MS (APCI⁺) m/e 451 (M+H)⁺.



Example 231

[4-(3-piperidinecarboxyamino)-2-phenylbenzoyl]methionine hydrochloride

Example 231A

1-tert-butoxycarbonylpiperidine-3-carboxylic acid

To a mixture of piperidine-3-carboxylic acid (1.29 g, 10 mmol) in THF (20 mL) was added aqueous 4N sodium hydroxide (5 mL) and di-tert-butylidicarbonate (2.62 g, 12 mmol) and the reaction mixture was stirred for 6 hours. The reaction mixture was acidified with 3N HCl (7 mL) and extracted three times with ethyl acetate. The combined organic extracts were washed with water (2x) and brine, dried, filtered, and concentrated *in vacuo* to give 1-tert-butoxycarbonylpiperidine-3-carboxylic acid (2.11 g) as a white solid.

Example 231B

[4-(1-*tert*-butoxycarbonylpiperidin-3-ylcarboxyamino)-2-phenylbenzoyl]methionine methyl ester

The desired compound was prepared by coupling of the product of Example 231A and (4-amino-2-phenylbenzoyl)methionine methyl ester (compound 8) according to the method of Example 186C.

Example 231C

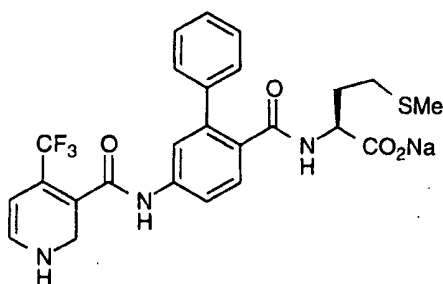
[4-(1-*tert*-butoxycarbonylpiperidin-3-ylcarboxyamino)-2-phenylbenzoyl]methionine

The desired compound was prepared by saponification of the product of Example 231B according to the procedure of Example 159.

Example 231D

[4-(3-piperidinecarboxyamino)-2-phenylbenzoyl]methionine hydrochloride

The product of Example 231C was deprotected with 4N HCl-dioxane using the procedure of Example 229B. ¹H nmr (300 MHz, D₂O) δ 7.37 - 7.60 (m, 8H), 4.44 (dd, 1H), 3.46 (dd, 1H), 3.31 (m, 2H), 1.14 (m, 1H), 3.02 (m, 1H), 1.71 - 2.11 (m, 8H), 2.02 (s, 3H). MS (CI NH₃) M/e 456 (M+H⁺, 438, 408, 339, 307, 196. Anal calcd for C₂₄H₃₀ClN₃O₄S•2.54 H₂O: C, 53.60; H, 6.57; N, 7.59. Found: C, 53.60; H, 6.19; N 7.59.



Example 283

[4-(1H-4-trifluoromethyl-1,2-dihydropyrid-3-ylcarbonylamino)-2-phenylbenzoyl]methionine sodium salt

Example 283A

(4-nitro-2-phenylbenzoyl)methionine 2-trimethylsilylethyl ester

A mixture of (4-nitro-2-phenylbenzoyl)methionine methyl ester (7.69 g, 30 mmol), prepared as in Example 192A and aqueous saturated lithium hydroxide (20 mL) in methanol (50 mL) was refluxed for 6 hours. The reaction mixture was carefully acidified with

concentrated hydrochloric acid (10 mL), and extracted with ethyl acetate (4x). The combine extracts were washed with brine, dried over anhydrous magnesium sulfate, filtered and concentrated *in vacuo*. The residue was dissolved in dichloromethane (50 mL) and THF (10 mL) and 2-trimethylsilylethanol (3.72 g, 31.5 mmol), 1,3-diisopropylcarbodiimide (5.17 mL, 33 mmol) and 4-dimethylaminopyridine (30 mg) were added sequentially. After 4 hours, aqueous hydrochloric acid (0.1 N, 0.5 mL) was added and the reaction mixture was stirred for another 2 hours. The reaction mixture was then filtered through silica gel (40 g), and the filtrate was concentrated *in vacuo*. The residue was purified by column chromatography (5% ethyl ether-hexane) to give the title compound (8.90 g, 87%).

Example 283B

(4-amino-2-phenylbenzoyl)methionine 2-trimethylsilylethyl ester

A mixture of the product of Example 283A (8.85 g, 25.8 mmol), ammonium formate (4.88 g, 77.4 mmol) and palladium (10%) on carbon (1 g) in methanol was refluxed for 5 hours. The mixture was then filtered through Celite and rinsed with ethyl acetate. The filtrate was diluted with ethyl acetate, washed with water and brine, dried over anhydrous sodium sulfate, filtered and concentrated *in vacuo* to give the title compound which was used without further purification.

Example 283C

4-(4-trifluoromethylpyrid-3-ylcarbonylamino)-2-phenylbenzoic acid 2-trimethylsilylethyl ester

A mixture of 4-trifluoromethylnicotinic acid (472 mg, 2.46 mmol), the product of Example 283B (771 mg, 2.46 mmol), 3-hydroxy-1,2,3-benzotriazin-4(3H)-one (481 mg, 2.95 mmol), 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide (566 mg, 2.95 mmol) in DMF (8 mL) was stirred room temperature for 15 hours. The reaction mixture was diluted with ethyl acetate (100 mL), washed with water and brine, dried over anhydrous magnesium sulfate, filtered and concentrated *in vacuo*. The residue was purified by column chromatography (30% ethyl acetate-hexane) to give the title compound (1.04 g, 87%).

Example 283D

4-(1H-4-trifluoromethyl-1,2-dihydropyrid-3-ylcarbonylamino)-2-phenylbenzoic acid 2-trimethylsilylethyl ester

A solution of the product of Example 283C (1.02 g, 2.09 mmol), tetrabutylammonium borohydride (539 mg, 2.1 mmol) in 1,2-dichloroethane (10 mL) was heated at 80 °C for 6 hours. The reaction mixture was diluted with ethyl acetate, washed with saturated sodium bicarbonate, water and brine, dried over anhydrous magnesium

sulfate, filtered and concentrated *in vacuo*. The residue was purified by column chromatography (30% ethyl acetate-hexane) to give the title compound (247 mg, 24%).

Example 283E

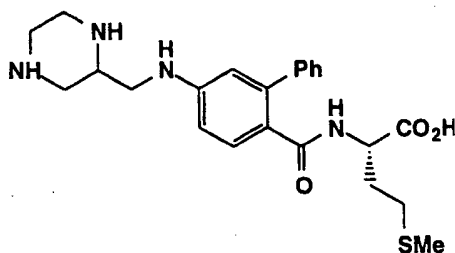
[4-(1H-4-trifluoromethyl-1,2-dihydropyrid-3-ylcarbonylamino)-2-phenylbenzoyl]methionine methyl ester

A solution of the product of Example 283D (227 mg, 0.48 mmol) and tetrabutylammonium fluoride (261 mg, 1.0 mmol) in dioxane was heated at 80 °C for 90 min. The solvent was then evaporated, and the residue was further dried under high vacuum (2 mmHg) for 1 hour. To the residue was added *L*-methionine methyl ester hydrochloride (115 mg, 0.58 mmol), 3-hydroxy-1,2,3-benzotriazin-4(3*H*)-one (163 mg, 1.0 mmol), 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide (192 mg, 1.0 mmol), DMF (5 mL) and triethylamine (0.3 mL). After 15 hours, the reaction mixture was diluted with ethyl acetate, washed with water and brine, dried over anhydrous magnesium sulfate, filtered and concentrated *in vacuo*. The residue was purified by column chromatography (50% ethyl acetate-hexanes) to give the title compound (179 mg, 69%).

Example 283F

[4-(1H-4-trifluoromethyl-1,2-dihydropyrid-3-ylcarbonylamino)-2-phenylbenzoyl]methionine sodium salt

The desired compound was prepared by saponification of the product of Example 283E using the procedure of Example 276. ¹H NMR (300 MHz, DMSO-*d*₆) δ 9.67 (s, 1H), 8.87 (br s, 1H), 7.68 (m, 2H), 7.54 (s, 1H), 7.41-7.30 (m, 6H), 7.03 (dd, 1H), 6.51 (d, 1H), 4.67 (t, 1H), 4.48 (m, 1H), 3.78 (m, 1H), 2.14 (m, 2H), 1.96 (s, 3H), 1.77 (m, 2H). MS (APCI⁺) *m/e* 520 (M+H)⁺.



Example 286

[4-(2-piperazinylmethylamino)-2-phenylbenzoyl]methionine

Example 286A

di-tert-butyloxycarbonylpiperidine-2-carboxylic acid

Di-tert-butyl dicarbonate (15.5 g, 70.2 mmol) was added to a solution of piperazine-2-carboxylic acid (4.85 g, 23.4 mmol) and NaOH (98 mL of a 1 M aqueous solution, 98 mmol) in THF (100 mL). The cloudy mixture was stirred for 16 hours and then was concentrated under reduced pressure to remove THF. The aqueous solution was saturated with NaHCO₃ (s) and then extracted with ether (2x). The aqueous layer was cooled to 0 °C and then adjusted to pH 3 with 2 M aqueous HCl during which time a precipitate formed. The mixture was extracted with CH₂Cl₂ (3x), and the organic extracts were dried (MgSO₄) and concentrated under reduced pressure to provide the desired compound (7.61 g, 98% as a tan solid.

Example 286B

di-tert-butyloxycarbonylpiperidine-2-carboxylic acid N-methyl N-methoxy amide

Triethylamine (1.75 g, 17.1 mmol) was added dropwise to a solution of N,O-dimethylhydroxylamine hydrochloride (0.741 g, 7.44 mmol), the product of Example 286A (2.46 g, 7.44 mmol), 3-hydroxy-1,2,3-benzotriazin-4(3H)-one (1.61 g, 9.67 mmol), and 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide (1.89 g, 9.67 mmol) in DMF (75 mL). The reaction mixture was stirred at ambient temperature for 20 hours and then concentrated under reduced pressure (50 °C, 0.1 mm Hg). The residue was dissolved in ethyl acetate (70 mL), and the solution was extracted with saturated aqueous NaHCO₃ (3x) and brine. The organic phase was dried (MgSO₄) and concentrated to provide a golden wax. Flash column chromatography (20% ethyl acetate-hexane) afforded the desired compound (2.29 g) which was shown to be 78% pure by ¹H NMR.

Example 286C

di-tert-butyloxycarbonylpiperidine-2-carboxaldehyde

A solution of the product of Example 286B (0.971 g, 2.81 mmol) in THF (4 mL) was added dropwise to a slurry of LAH (0.112 g, 2.81 mmol) in THF (4 mL) at -50 °C. After 10 minutes the bath temperature was adjusted to -10 °C for 10 min and then returned to -50 °C. The addition of saturated aqueous KHSO₄ (8 mL) produced vigorous gas evolution, after which reaction mixture was allowed to warm to ambient temperature over 20 minutes and then filtered through Celite. The filtrate was extracted with 1 N HCl (2x), saturated aqueous NaHCO₃ (2x) and finally brine. The organic phase was dried (MgSO₄) and concentrated to provide the desired compound (0.304 g, 41%) as an amber oil.

Example 286D

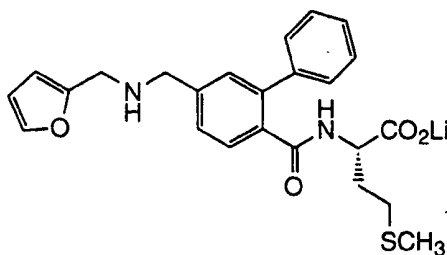
[4-(di-*tert*-butoxycarbonylpiperazin-2-yl)methylamino)-2-phenylbenzoyl]methionine methyl ester

The aldehyde prepared in Example 286C (0.599 g, 1.71 mmol) was added to a solution of *N*-(4-amino-2-phenylbenzoyl)methionine methyl ester hydrochloride (1.01 g, 2.05 mmol), prepared as in Example 192B, sodium acetate (0.425 g, 5.13 mmol) and acetic acid (0.205 g, 3.42 mmol) in isopropanol (7 mL). After 1 hour, Na(CN)BH₃ (0.147 g, 2.22 mmol) was added in two portions and the mixture was stirred for 15 hours before concentration under reduced pressure provided a waxy residue. Flash column chromatography (hexane-ethyl acetate-triethylamine 60:38:2) followed by radial chromatography eluting with 40% ethyl acetate-hexane) afforded the title compound (0.344 g, 31%) as a white foam. ¹H NMR (CDCl₃): δ 1.35-1.52 (comp, 18H), 1.52-1.71 (m, 1 H), 1.71-1.93 (m, 1 H), 2.02 (s, 3 H), 2.02-2.20 (comp, 2 H), 2.80-3.12 (comp, 2 H), 3.12-3.33 (br, 1 H), 3.33-3.50 (br, 1 H), 3.64 (s, 3 H), 3.83-4.28 (br, 3 H), 4.28-4.45 (br, 1 H), 4.60-4.72 (br, 1 H), 5.63-5.74 (br, 1 H), 6.44-6.58 (br, 1 H), 6.58-6.80 (br, 1 H), 7.33-7.52 (comp, 5 H), 7.72 (d, 1 H). LRMS (CI): 657 (M+1)⁺.

Example 286E

[4-(2-piperazinyl)methylamino)-2-phenylbenzoyl]methionine

Sodium hydroxide (0.642 mL of a 0.979 M aqueous solution, 0.629 mmol) was added to a solution of the product of Example 286D (0.344 g, 0.524 mmol) in methanol (2 mL). After 5 hours the mixture was lyophilized, and the resulting white foam was treated with HCl (4.7 mL of a 4 M dioxane solution, 18.8 mmol). After 7 hours, pentane was added and the yellow precipitate was isolated by filtration to afford the desired compound (79.3 mg, 24%) as the bis-hydrochloride, mono-sodium chloride salt. ¹H NMR (300 MHz, CD₃OD) δ 1.71-1.85 (m, 1H), 1.91-2.00 (m, 1H), 2.02 (s, 3H), 2.02-2.15 (m, 1H), 2.15-2.27 (m, 1H), 3.32-3.56 (comp, 3H), 3.56-3.75 (comp, 4H), 3.75-3.96 (br, 2H), 4.45 (dd, 1H), 6.73 (s, 1H), 6.81 (d, 1H), 7.30-7.50 (comp, 6H). LRMS (CI) m/e 443 (M+H)⁺.



Example 302

[4-(2-furylmethylaminomethyl)-2-phenylbenzoyl]methionine lithium salt

7435

Example 302A4-(2-furylmethylaminomethyl)-2-phenylbenzoic acid methyl ester

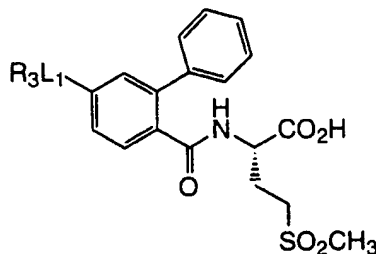
To a stirred solution of 4-carboxaldehyde-2-phenylbenzoic acid methyl ester (0.73 g, 3.0 mmol), prepared as in Example 160B, in methanol (15 mL) was added furfurylamine (0.33 g, 3.4 mmol), sieves (~ 1g), NaBH₃CN (0.29 g, 4.6 mmol) and acetic acid (~0.3 mL) to pH = 6. The mixture was stirred for 3 hours at ambient temperature. The reaction was concentrated in vacuo and the residue was taken up in ethyl acetate and filtered through a short bed of silica gel. The bed was washed with ethyl acetate and the filtrate concentrated in vacuo. The residue was purified by flash chromatography (CH₂Cl₂-ethyl acetate 9:1) to give the desired compound (0.72 g, 73%) as an opaque yellow paste.

Example 302B[4-(2-furylmethylaminomethyl)-2-phenylbenzoyl]methionine methyl ester

The desired compound was prepared by saponification of the product of Example 302A, followed by coupling with methionine methyl ester hydrochloride according to the method of Examples 299C and D.

Example 302C[4-(2-furylmethylaminomethyl)-2-phenylbenzoyl]methionine methyl ester

To a stirred solution of the product of Example 302B (56 mg, 0.12 mmol) in THF (2 mL) was added a solution of LiOH·H₂O (5.5 mg, 0.13 mmol) in H₂O (1 mL) and the resulting solution stirred for 3 hours at ambient temperature. The reaction was concentrated in vacuo, diluted with H₂O, filtered and lyophilized to give the title compound (57 mg, 97%) as a white powder. ¹H NMR (300 MHz, DMSO-d₆, 90 °C) δ 7.48-7.24 (m, 9H), 7.07-7.04 (m, 1H), 6.37-6.34 (m, 1H), 6.24-6.20 (m, 1H), 3.76-3.69 (m, 5H), 2.43-2.16 (m, 3H), 2.00-1.66 (m, 5H). MS *m/z* 439 (M+1)⁺. Anal calcd for C₂₄H₂₅LiN₂O₄S·2 H₂O (480.50): C, 59.99; H, 6.08; N, 5.83. Found: C, 59.83; H, 5.83; N, 5.74.



7465

Examples 350-357

All reactions were performed either in a Manual solid phase synthesis flask using a 1200 rotary shaker or on an Advanced ChemTech Model 396 Multiple Peptide Synthesizer (Advanced ChemTech Inc.; Louisville, Kentucky) at ambient temperature.

7470 After the reactions were performed the finished compounds were cleaved from the resin. Usually, 80-90 mg of the dried resin containing the desired amide; urea; or secondary amine was treated with a 1.50 mL solution of 95/5 (v:v) trifluoroacetic acid/water for 1.5 h at ambient temperature. The spent resin was removed by filtration and the resulting cleavage solution evaporated in-vacuo. In most cases, 5- 20 mg of crude compound was obtained.

7475 Compounds obtained had the desired MW as determined by electrospray mass spectroscopy and had an HPLC purity of 40-90%, or were further purified by partition chromatography to afford compounds of 40-60% HPLC purity. Two types of gradients were used for the reverse phase HPLC. For the amides and ureas a gradient starting with 100% water-0.1% Trifluoroacetic acid and finishing with 100% acetonitrile-0.1% Trifluoroacetic acid during a 30

7480 minute period was used. For the secondary amines a gradient beginning with 100% water-5mmol ammonium acetate and finishing with 80% acetonitrile-water-5mmol ammonium acetate during 25 minutes was used.

80 mg of resin (substitution 0.40 mmol/g) containing [4-amino-2-phenylbenzoyl]methionine-Wang-polystyrene resin was shaken for 3 min. with 1.0 mL. of

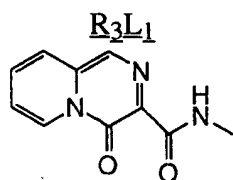
7485 N-methylpyrrolidone (NMP). The solvent was drained and the resin was treated 2x (3 min) with 1 mL. NMP. To the now swollen resin were then added 0.20 mL NMP; 0.20 mL of a 1.92 M diisopropylethylamine (DIEA)/NMP solution (15 eq.); 1.00 mL of a 0.180 mM/NMP solution of the desired carboxylic acid (5 eq.); and finally 0.20 mL of a 0.90 M Bromo-tris-pyrrolidino-phosphonium hexafluorophosphate (PyBrop; 5 equiv.)1/NMP

7490 solution. The reaction slurry was then mixed for 6 h and drained. The resin was then washed with NMP (3x; 1.0 mL; 3 min. ea); isopropanol (IPA; 5x; 1.0 mL; 3 min. ea.); NMP (3x; 1.0 mL; 3 min. ea.); methanol (MEOH; 2x; 1.0 ml; 3 min. ea.); and finally diethyl ether (2x; 1.0 mL; 3 min. ea.). The resin was then dried and subjected to cleavage conditions described above.

7495

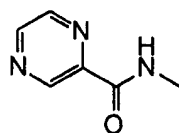
Example

354

MS (M+H)⁺

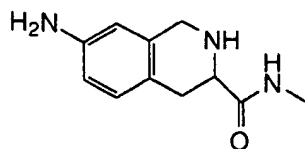
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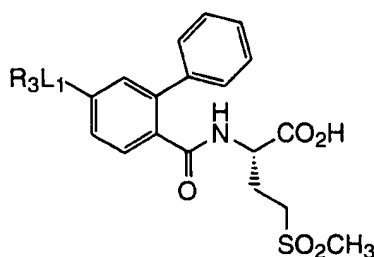


451

356



519

Examples 358

7500 90 mg of resin (substitution 0.39 mmol/g.) containing [4-amino-2-phenylbenzoyl]methionine-Wang-polystyrene resin was shaken with 1.0 mL dimethylformamide (DMF) for 3 min. The solvent was drained and the resin was then washed with DMF (3x; 1.0 mL; 3 min. ea.); tetrahydrofuran (THF; 4x; 1.0 mL; 3 min. ea.); THF/dichloromethane (DCM) 1:1 (v:v) (4x; 1.0 mL; 3 min. ea.). The resin was then treated

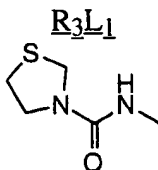
7505 with 0.20 mL of DCM/THF (1:1) and a 1.0 mL solution of 0.50 M p-Nitrophenylchloroformate/0.50 M DIEA in a 1:1 solvent mixture of DCM/THF. The resin suspension was then shaken for 15 min. and to the suspension was then added .020 mL of neat DIEA. After shaking for an additional 15 min.; the solvents were drained away and the resin was then washed with DCM/THF (1:1) (4x; 1.0 mL; 3 min. ea.) The resin was then

7510 treated with 0.20 mL of DMF and 1.0 mL of a DMF solution containing 0.50 M of the desired primary or secondary amine and 0.50 M of DIEA. The suspension was shaken for 30 min. The solvent was drained off and the resin was then washed with DMF (4x; 1.0 mL; 3 min. ea); THF (4x; 1.0 mL; 3 min. ea.); DCM/THF (4x; 1.0 mL; 3 min. ea); diethyl ether (4x; 1.0 mL; 3 min. ea.). The resin was then dried and subjected to cleavage from the resin

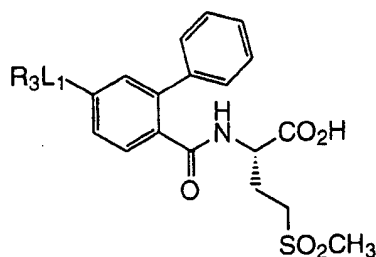
7515 as described above.

Example

358

MS (M+H)⁺

460

Examples 360-362Examples 364-366Examples 369-374Examples 377-378Example 381

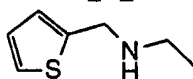
7525 Typically 80 mg of resin (substitution of 0.40 mmol/g) containing 4-formyl-2-phenylbenzamide-L-Methionine-Wang-polystyrene resin was swollen with 1.0 mL of dimethyl acetamide (DMA) for 3 min. The solvent was drained and the resin was then washed with additional DMA (2x; 1.0 mL; 3 min. ea.). The resin was then suspended in 0.20 mL of DMA and to the suspension was then added a 1.0 mL solution containing 0.48

7530 mM of the desired primary amine (10 eq.) in a 3:1 (v:v) solution of DMA/acetic acid. The resin was shaken for 2 h and was then treated with 0.25 mL of a 2.4 mM solution of sodium cyanoborohydride (10 eq.) in DMA. The resin-slurry was shaken for an additional 2 h. The solvents were drained and the resin was then washed with DMA (6x; 1.0 mL; 3 min. ea.); DMF (6x; 1.0 mL; 3 min. ea.); IPA (6x; 1.0 mL; 3 min. ea.); DMF (6x; 1.0 mL; 3 min.

7535 ea.); MEOH (6x; 1.0 mL; 3 min. ea.); diethyl ether (6x; 1.0 mL; 3 min. ea.). The resin was dried and then subjected to cleavage as described above.

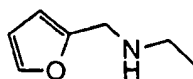
ExampleR₃L₁MS (M+H)[±]

360



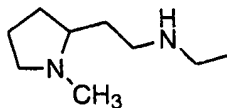
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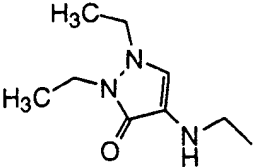
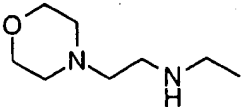
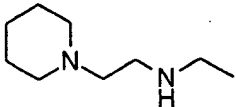
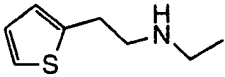
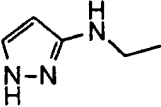
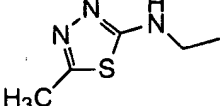
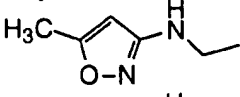
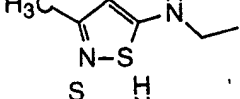
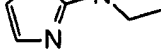
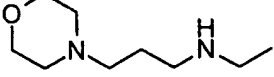
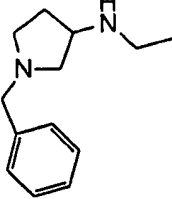
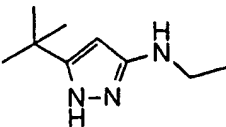


439

362



471

364		498
365		473
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369		470
370		425
371		458
372		441
373		457
374		443
377		487
378		573
381		481

7540

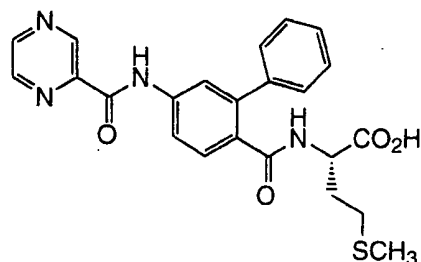
Examples 395 and Example 398

The following compounds were prepared using the materials and methods described above.

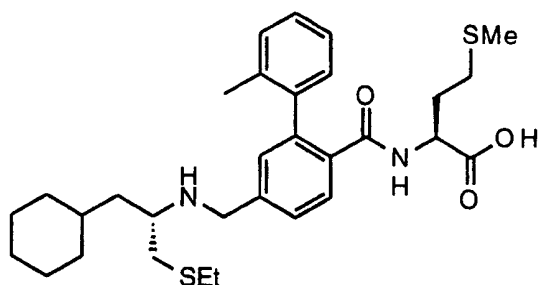
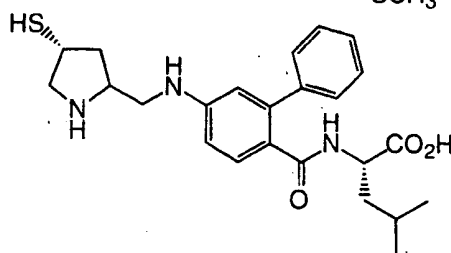
7545

Example

395



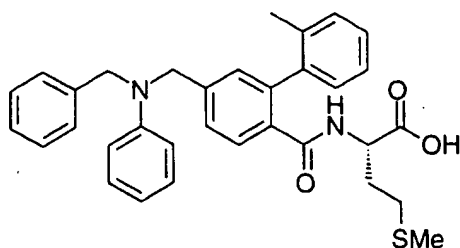
398

Example 403

7550 [4-(1-ethylthio-3-cyclohexylprop-2-ylaminomethyl)-2-(2-methylphenyl)benzoyl] methionine.

The desired compound was prepared according to the method of Example 349A except substituting (S)-(+)-1-ethylthio-3-cyclohexyl-2-propylamine hydrochloride for (S)-(+)-2-amino-3-cyclohexyl-1-propanol hydrochloride. ¹H NMR (DMSO-d₆, 300 MHz) δ 8.02 (m, 1H), 7.50-7.38 (m, 2H), 7.22-7.05 (m, 4H), 4.21 (m, 1H), 3.88-3.78 (m, 2H), 2.74-2.60 (m, 2H), 2.51 (s, 3H), 2.44 (q, J=7.5 Hz, 2H), 2.22-1.95 (m, 5H), 1.88-1.50 (m, 7H), 1.45-1.25 (m, 4H), 2.21-1.02 (m, 3H), 1.12 (t, J=7.5 Hz, 3H), 0.90-0.70 (m, 2H). MS (CI/NH₃) m/e: 557 (M+H)⁺ Anal calcd for C₃₁H₄₄N₂O₃S₂ • 1.15 H₂O: C, 64.47; H, 8.08; N, 4.85. Found: C, 64.48; H, 7.84; N, 4.72.

7560

Example 4064-(N-benzyl-N-phenyl)-aminomethyl-2-(2-methylphenyl)benzoylmethionine

The desired compound was prepared according to Example 273 except substituting
 7565 N-benzylaniline for 2-thiophenemethanol in Example 273A.

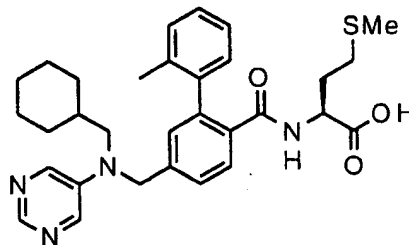
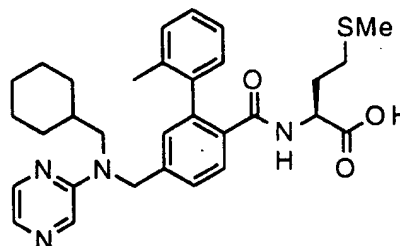
^1H NMR (CD_3OD): δ 1.62-1.77 (m, 1 H), 1.86-2.07 (comp, 7 H), 2.07-2.18 (comp, 2 H), 4.37-4.47 (br, 1 H), 4.70-4.84 (comp, 4 H), 6.68-6.89 (br, 3 H), 7.08-7.32 (comp, 13 H), 7.35-7.40 (m, 1 H), 7.56-7.62 (m, 1 H). LRMS (CI): 539 ($\text{M}+1$) $^+$.

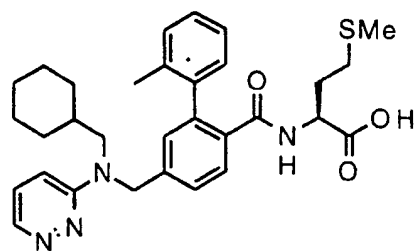
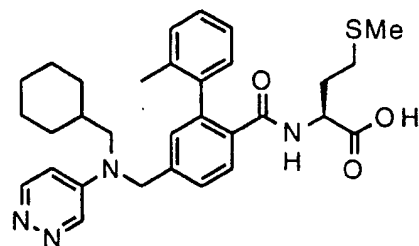
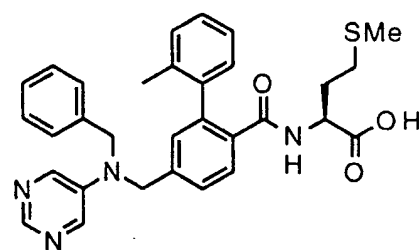
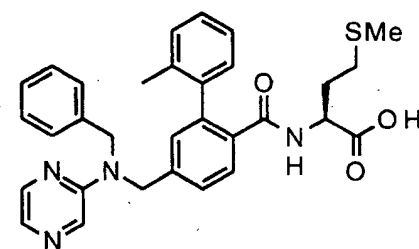
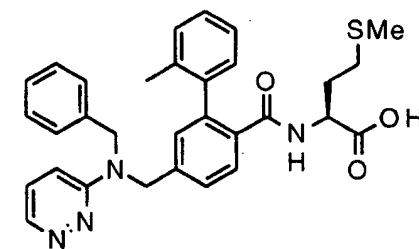
7570

Examples 411-417

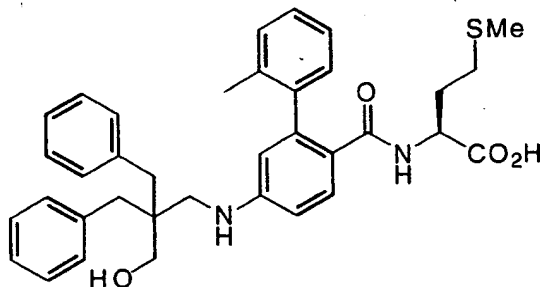
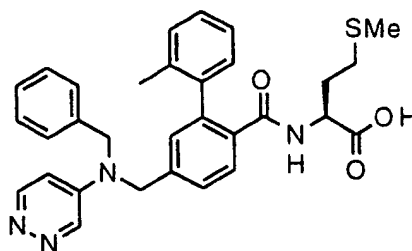
The following compounds are prepared according to the method of Example 407 except substituting the desired N-benzyl- or N-cyclohexylmethylaminopyridine for N-benzyl-3-aminopyridine.

7575

411412

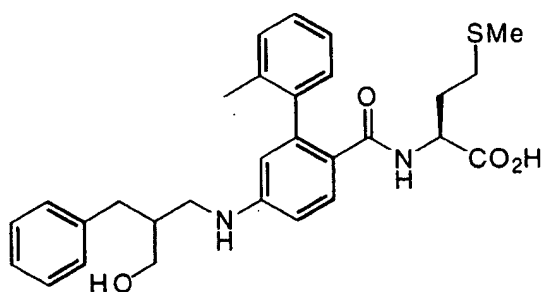
413414415416416A

417

Example 475

7580 N-[4-N-(2,2-dibenzyl-3-hydroxypropyl)amino-2-(2-methylphenyl)benzoyl]methionine
sodium salt

The desired compound was prepared according to the method of Examples 25A -25B
¹H nmr (300 MHz, DMSO-d₆): δ 7.40 (d, 1 H), 7.25-7.10 (m, 15 H), 6.65 (m, 1 H), 6.27
 (d, 1 H), 6.08 (m, 1 H), 4.84 (m, 1 H), 3.70 (m, 1 H), 3.17 (br s, 2 H), 3.03 (br s, 2 H),
 7585 2.80 (AB q, 4 H), 2.18 (m, 1 H), 1.99, 1.91 (2 br s's, 6 H), 1.97 (m, 1 H), 1.70-1.50 (m,
 2 H). MS (APCI +) m/e 597 (M+H)⁺.

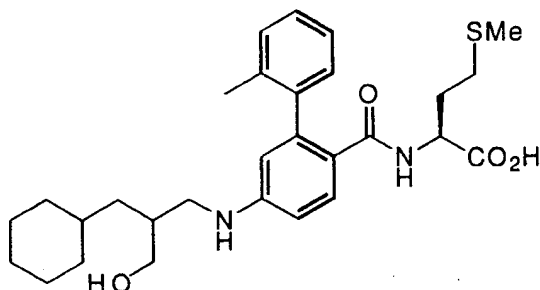
Example 476

7590 N-[4-N-(2-benzyl-3-hydroxypropyl)amino-2-(2-methylphenyl)benzoyl]methionine
sodium salt

The desired compound was prepared according to the method of Examples 25A -25B
¹H nmr (300 MHz, DMSO-d₆): δ 7.35 (d, 1 H), 7.28-7.10 (m, 10 H), 6.50 (m, 1 H), 6.16
 7595 (d, 1 H), 6.05 (m, 1 H), 4.55 (m, 1 H), 3.64 (m, 1 H), 3.39 (m, 2 H), 2.62 (m, 2 H), 2.38

(m, 1 H), 2.15 (m, 1 H), 1.97, 1.91 (2 br s's, 6 H), 1.95 (m, 2 H), 1.70-1.50 (m, 2 H)
(note: the methylene protons adjacent to the NH group might be buried in the residue water
pk of DMSO). MS (APCI +) m/e 506 (M+H)⁺.

7600

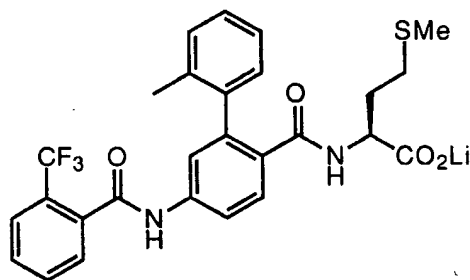
Example 479

N-[4-N-(2-cyclohexylmethyl-3-hydroxypropyl)amino-2-(2-
methylphenyl)benzoyl]methionine

7605

The desired compound was prepared according to the method of Examples 25A -25B
¹H nmr (300 MHz, DMSO-d₆): δ 7.37 (d, 1 H), 7.16 (m, 3 H), 7.02 (d, 1 H), 6.93 (m, 1
H), 6.58 (m, 1 H), 6.00 (m, 1 H), 4.45 (m, 1 H), 3.65 (m, 1 H), 3.38 (m, 2 H), 2.19 (m,
1 H), 2.03, 1.97, 1.93, 1.92 (4 s's, 6 H), 1.96 (M, 1 H), 1.90-0.75 (m's, 14 H). MS (ESI
-): m/e 511 (M-H)⁻.

7610

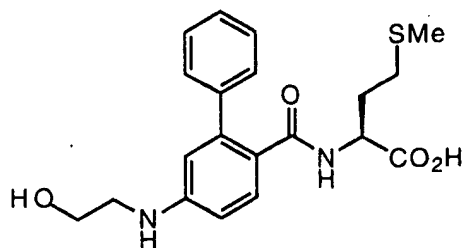
Example 481

N-[4-N-(4-trifluoromethylnicotinoyl)amino-2-(2-methylphenyl)benzoyl]methionine
lithium salt

7615

The desired compound was prepared according to the method of Example 57. ¹H
nmr (300 MHz, DMSO-d₆): δ 11.04 (br s, 1 H), 9.05 (s, 1 H), 8.98 (d, 1 H), 7.90 (d, 1
H), 7.69 (br d, 1 H), 7.57 (m, 2 H), 7.23 (m, 4 H), 6.97 (m, 1 H), 3.70 (m, 1 H), 2.20
(m, 1 H), 2.03 (m, 1 H), 1.91 (br s, 6 H), 1.70 (m, 1 H), 1.58 (m, 1 H). MS (ESI -): m/e
530 (M-H)⁻.

7620

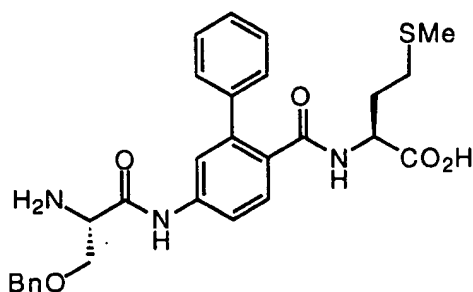
Example 502

7625

N-[4-N-2-hydroxyethylamino-2-phenylbenzoyl]methionine

The desired compound was prepared according to the method of Example 57, employing t-butyl bromoacetate. The resultant t-butyl ester was treated with TFA, and then reduced with borane. ¹H NMR (CD₃OD): δ 1.68-1.81 (m, 1 H), 1.89-2.10 (m, 1 H), 2.01 (s, 3 H), 2.02-2.24 (comp, 2 H), 3.28 (t, J = 5.9 Hz, 2 H), 3.72 (t, J = 5.9 Hz, 2 H), 4.44 (dd, J = 4.4, 9.2 Hz, 1 H), 6.57 (d, J = 2.3 Hz, 1 H), 6.65 (dd, J = 2.4, 8.5 Hz, 1 H), 7.28-7.44 (comp, 6 H). LRMS (CI): 389 (M+1)⁺

7630

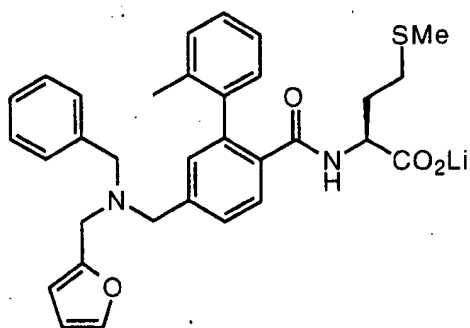
Example 503

7635

N-[4-(N-2-amino-3-benzyloxypropionyl)amino-2-phenylbenzoyl]methionine

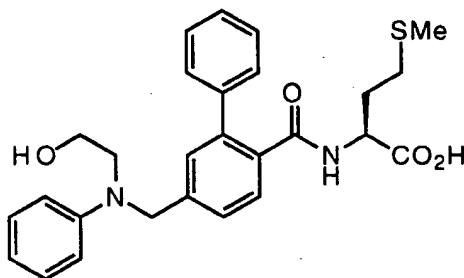
The desired compound was prepared according to the method of Example 57. ¹H NMR (CD₃OD): δ 1.71-1.88 (m, 1 H), 1.90-2.28 (comp, 6 H), 3.65-3.72 (m, 1 H), 3.86-3.94 (comp, 2 H), 4.24-4.31 (m, 1 H), 4.44-4.56 (m, 1 H), 4.62 (dd, J = 12.2, 29.2 Hz, 2 H), 7.23-7.58 (comp, 11 H), 7.62-7.70 (comp, 2 H). LRMS (CI): 522 (M+1 of free base)⁺

7640

Example 504

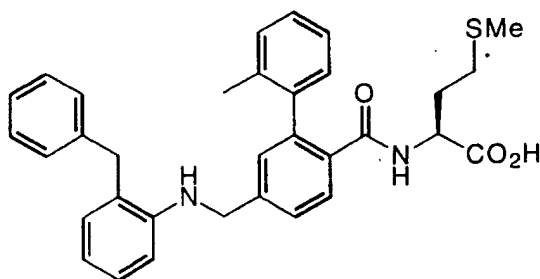
7645 N-[4-N-(furan-2-ylmethyl)-N-benzylaminomethyl]-2-(2-methylphenyl)benzoyl]methionine
lithium salt

The desired compound was prepared according to the method of Example 158 ¹H NMR (CD₃OD): δ 1.57-1.70 (m, 1 H), 1.75-1.92 (comp, 2 H), 1.94-2.01 (comp, 6 H), 2.01-2.09 (br, 1 H), 3.56-3.67 (comp, 6 H), 4.17-4.29 (br, 1 H), 6.20-6.23 (m, 1 H),
 7650 6.33-6.36 (m, 1 H), 7.07-7.33 (comp, 8 H), 7.33-7.40 (comp, 2 H), 7.42-7.49 (comp, 2 H), 7.60-7.67 (m, 1 H). LRMS (CI): 543 (M+1 of protonated acid)⁺.

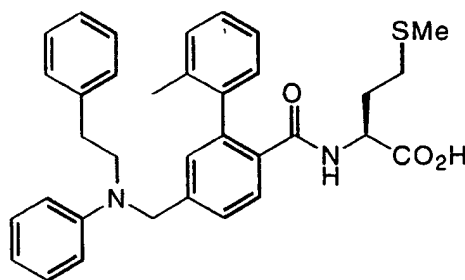
Example 505

N-[4-N-phenyl-N-benzylaminomethyl]-2-phenylbenzoyl]methionine

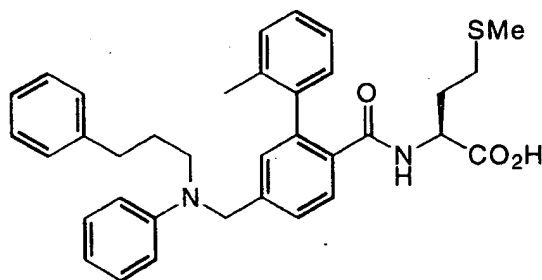
The desired compound was prepared according to the method of Example 157 ¹H NMR (d₆-DMSO): δ 1.73-1.96 (comp, 2 H), 1.99 (s, 3 H), 2.12-2.32 (comp, 2 H), 5.53-3.66 (comp, 2 H), 3.72-3.76 (br s, 1 H), 4.24-4.33 (comp, 2 H), 4.57-4.61 (br s, 1 H),
 7660 4.72 (s, 2 H), 6.58-6.96 (comp, 3 H), 7.06-7.19 (comp, 2 H), 7.25-7.42 (comp, 8 H), 8.53 (d, J = 7.7 Hz, 1 H). LRMS (CI): 479 (M+1)⁺.

Example 506N-[4-N-(2-benzylphenyl)aminomethyl-2-(2-methylphenyl)benzoyl]methionine

The desired compound was prepared according to the method of Example 157 ¹H NMR (CD₃OD): δ 1.63-1.80 (br, 1 H), 1.87-2.07 (br, 7 H), 2.07-2.23 (comp, 2 H), 4.02 (s, 2 H), 4.38-4.51 (comp, 3 H), 6.87-6.93 (br, 1 H), 6.96-7.44 (comp, 14 H), 7.58-7.64 (m, 1 H). LRMS (CI): 539 (M+1)⁺, 556 (M+NH₄)⁺.

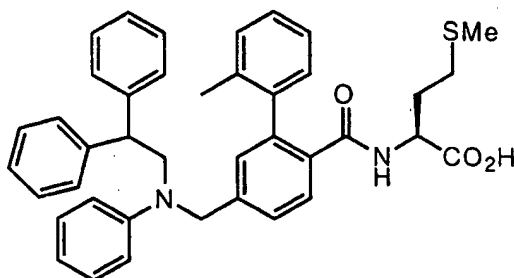
Example 507N-[4-N-(2-phenylethyl)-N-phenylaminomethyl-2-(2-methylphenyl)benzoyl]methionine

The desired compound was prepared according to the method of Example 157 ¹H NMR (CD₃OD): δ 1.55-1.68 (m, 1 H), 1.71-2.12 (comp, 9 H), 2.92 (t, 2 H), 3.63-3.71 (m, 2 H), 4.16-4.27 (br, 1 H), 4.52 (s, 2 H), 6.64 (t, 1 H), 6.74 (d, 2 H), 6.99-7.30 (comp, 13 H), 7.60 (d, 1 H). LRMS (ESI⁻): 551 (M-1)⁻.

Example 508N-[4-N-(3-phenylpropyl)-N-phenylaminomethyl-2-(2-methylphenyl)benzoyl]methionine

7685 The desired compound was prepared according to the method of Example 157 ¹H NMR (CD₃OD): δ 1.45-1.62 (m, 1 H), 1.63-2.05 (comp, 11 H), 2.52-2.61 (m, 1 H), 3.30-3.39 (m, 2 H), 4.08-4.19 (br, 1 H), 4.50 (s, 2 H), 6.49-6.56 (comp, 3 H), 6.92-7.23 (comp, 13), 7.49-7.56 (m, 1 H). LRMS (ESI⁻): 565 (M-1)⁻.

7690

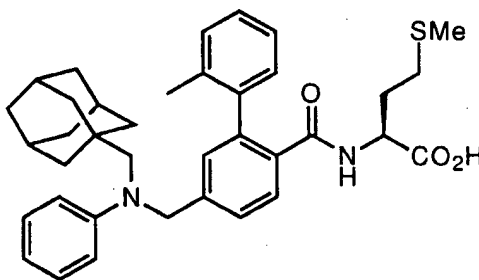


Example 509

N-[4-N-(2,2-diphenyl)ethyl-N-phenylaminomethyl]-2-(2-methylphenyl)benzoyl]methionine

7695 The desired compound was prepared according to the method of Example 157 ¹H NMR (d₆-DMSO): δ 1.46-2.02 (comp, 10 H), 3.38-3.42 (m, 1 H), 3.61-3.73 (br, 1 H), 4.16 (d, *J* = 7.3 Hz, 2 H), 4.31 (s, 2 H), 4.40-4.47 (m, 1 H), 6.55-6.67 (comp, 3 H), 6.78 (s, 1 H), 6.82-6.94 (br, 1 H), 7.05-7.21 (comp, 8 H), 7.22-7.30 (comp, 4 H), 7.35-7.41 (comp, 5 H). LRMS (CI): 629 (M+1)⁺.

7700

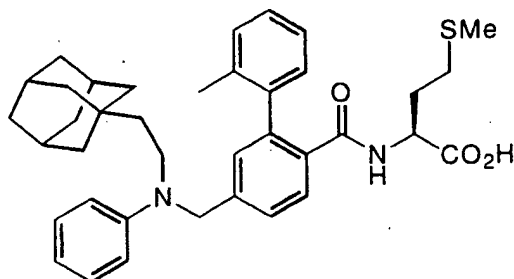


Example 510

N-[4-N-(adamantan-1-ylmethyl)-N-phenylaminomethyl]-2-(2-methylphenyl)benzoyl]methionine

7705 The desired compound was prepared according to the method of Example 157 ¹H NMR (d₆-DMSO): δ 1.48-2.20 (br, comp, 25 H), 3.16-3.31 (br m, 1 H), 3.40-4.30 (br comp, 4 H), 4.65-4.74 (br m, 1 H), 6.49-6.57 (br m, 1 H), 6.68-6.75 (br comp, 2 H), 6.85-7.12 (br comp, 3 H), 7.14-7.25 (br comp, 5 H), 7.45 (d, *J* = 8.0 Hz, 1 H). LRMS (CI): 597 (M+1)⁺.

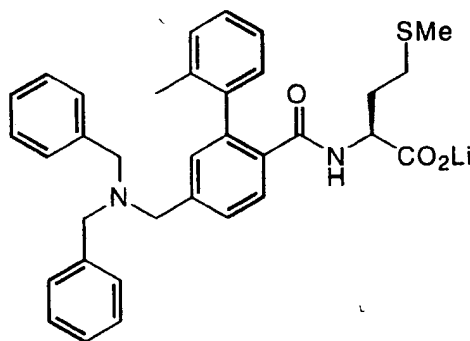
7710

Example 511N-[4-N-(2-adamantan-1-ylethyl)-N-phenyl]aminomethyl-2-(2-methylphenyl)benzoyl]methionine

7715

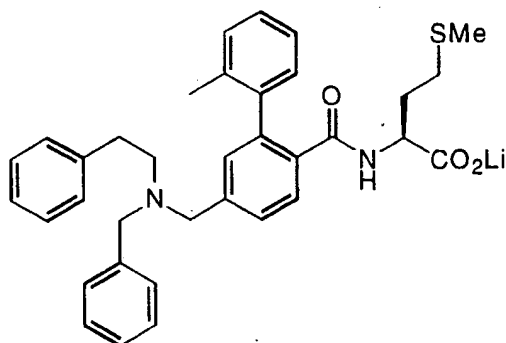
The desired compound was prepared according to the method of Example 157 ¹H NMR (d₆-DMSO): δ 1.28-1.37 (comp, 2 H), 1.47-1.71 (comp, 15 H), 1.88-2.10 (comp, 11 H), 3.33-3.47 (br comp, 2 H), 3.61-3.69 (br m, 1 H), 4.54 (s, 2 H), 6.55 (t, J= 7.1 Hz, 1 H), 6.63 (d, J= 8.1 Hz, 2 H), 6.88-6.94 (br m, 1 H), 6.97 (d, J= 1.3 Hz, 1 H), 7.07-7.21 (comp, 5 H), 7.27 (dd, J= 1.7, 7.8 Hz, 1 H), 7.49 (d, J= 8.2 Hz, 1 H). LRMS (ESI⁻): 609 (M-1)⁻.

7720

Example 512N-[4-N,N-dibenzylaminomethyl-2-(2-methylphenyl)benzoyl]methionine lithium salt

The desired compound was prepared according to the method of Example 158 ¹H NMR (d₆-DMSO): δ 1.44-2.17 (comp, 10 H), 3.33-3.77 (comp, 7H), 6.90-7.56 (comp, 17 H). LRMS (ESI⁻): 551 (M-1 of protonated acid)⁻.

7730

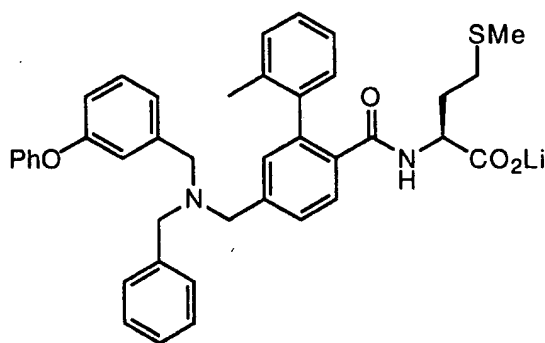
Example 513N-[4-N-(2-phenylethyl)-N-benzylaminomethyl]-2-(2-methylphenyl)benzoyl]methionine

7735

lithium salt

The desired compound was prepared according to the method of Example 158 ¹H NMR (d₆-DMSO): δ 1.65-1.90 (comp, 2 H), 1.96 (s, 3 H), 1.98-2.24 (comp, 5 H), 3.04-3.20 (comp, 4 H), 4.17-4.32 (br, 1 H), 4.36-4.56 (br, 4 H), 7.03-7.34 (comp, 12 H), 7.43-7.53 (br, 3 H), 7.54-7.63 (comp, 2 H), 7.67-7.76 (comp, 2 H), 7.76-7.84 (m, 1 H), 8.32 (d, *J* = 7.3 Hz, 1 H), 11.42-11.64 (br, 1 H), 12.35-12.55 (br, 1 H). LRMS (CI): 567 (M+1)⁺.

7740

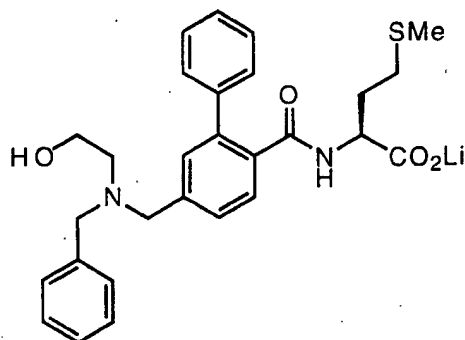


7745

Example 514N-[4-N-(3-phenoxybenzyl)-N-benzylaminomethyl]-2-(2-methylphenyl)benzoyl]methioninelithium salt

The desired compound was prepared according to the method of Example 158 ¹H NMR (d₆-DMSO): δ 1.65-1.90 (comp, 2 H), 1.95 (s, 3 H), 1.96-2.22 (comp, 5 H), 3.42-3.58 (br, 2 H), 4.15-4.39 (comp, 5 H), 6.88-7.62 (comp, 19 H), 7.64-7.71 (m, 1 H), 8.05-8.22 (m, 1 H), 11.30-11.44 (br, 1 H). LRMS (CI): 645 (M+1)⁺.

7750

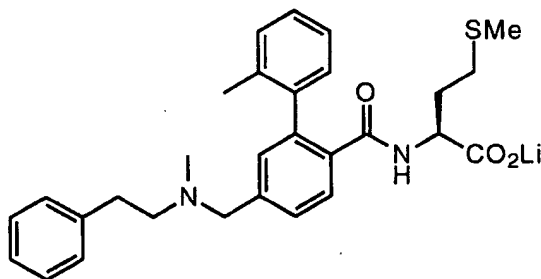


7755

Example 515N-[4-N-(2-hydroxyethyl)-N-benzylaminomethyl]-2-phenylbenzoyl]methionine lithium salt

The desired compound was prepared according to the method of Example 158 ¹H NMR (d₆-DMSO): δ 1.75-1.97 (comp, 2 H), 2.00 (s, 3 H), 2.15-2.34 (comp, 2 H), 3.00-3.11 (br m, 2 H), 3.79-3.87 (br m, 2 H), 4.28-4.51 (comp, 5 H), 7.32-7.43 (comp, 3 H), 7.43-7.55 (comp, 6 H), 7.64-7.79 (comp, 4 H), 8.66 (d, J = 7.7 Hz, 1 H). LRMS (CI): 493 (M+1)⁺.

7760

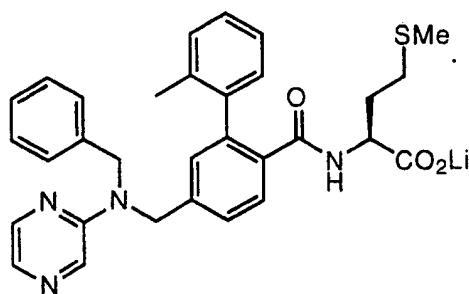


7765

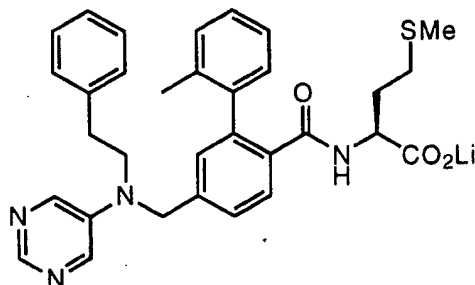
Example 516N-[4-N-methyl-N-(2-phenylethyl)aminomethyl]-2-(2-methylphenyl)benzoyl]methionine lithium salt

The desired compound was prepared according to the method of Example 158 ¹H NMR (d₆-DMSO): δ 1.65-1.91 (comp, 2 H), 1.96 (s, 3 H), 1.99-2.28 (comp, 5 H), 2.75 (s, 1 H), 3.05-3.25 (comp, 2 H), 3.25-3.44 (comp, 2 H), 4.17-4.30 (br, 1 H), 4.30-4.40 (m, 1 H), 4.46-4.56 (m, 1 H), 7.07-7.38 (comp, 9 H), 7.47-7.60 (comp, 2 H), 7.68-7.75 (m, 1 H), 8.33 (d, J = 7.0 Hz, 1 H), 11.10-11.26 (br, 1 H), 12.50-12.86 (br, 1 H). LRMS (CI): 491 (M+1)⁺.

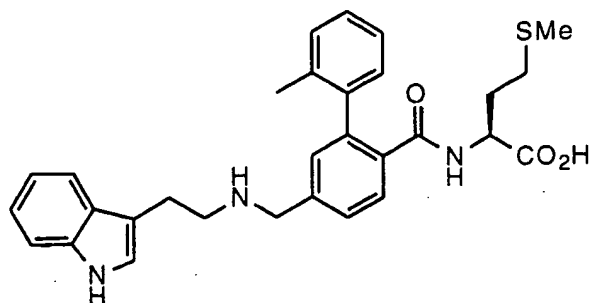
7775

Example 517N-[4-N-benzyl-N-pyrazin-2-ylaminomethyl-2-(2-methylphenyl)benzoyl]methionine lithium salt

7780 The desired compound was prepared according to the method of Example 157 ¹H NMR (d₆-DMSO): δ 1.46-2.09 (comp, 10 H), 3.59-3.70 (br, 1 H), 4.83-4.95 (comp, 4 H), 6.90-6.95 (br, 1 H), 7.00 (s, 1 H), 7.04-7.34 (comp, 10 H), 7.49 (d, J= 8.1 Hz, 1 H), 7.80 (d, J= 2.6 Hz, 1 H), 8.04-8.05 (m, 1 H), 8.07-8.10 (m, 1 H). LRMS (ESI⁻): 539 (M-1 of protonated acid)⁻.

Example 518N-[4-N-(2-phenylethyl)-N-pyrimidin-5-ylaminomethyl-2-(2-methylphenyl)benzoyl]methionine lithium salt

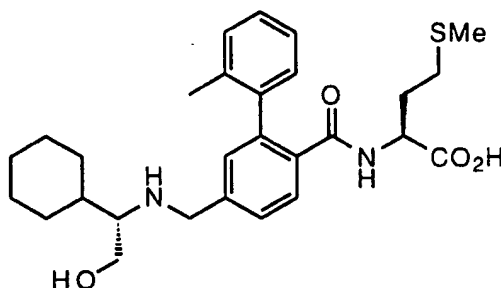
7790 The desired compound was prepared according to the method of Example 157 ¹H NMR (d₆-DMSO): δ 1.46-2.05 (comp, 10 H), 2.88 (t, J= 7.5 Hz, 2 H), 3.56-3.65 (br, 1 H), 3.73 (t, J= 7.5 Hz, 2 H), 4.66 (s, 2 H), 6.90-7.01 (br comp, 2 H), 7.05-7.31 (comp, 10 H), 7.49 (d, J= 7.8 Hz, 1 H), 8.23 (s, 2 H), 8.41 (s, 1 H). LRMS (ESI⁻): 553 (M-1 of protonated acid)⁻.

Example 519

7800 N-[4-N-(2-indol-3-ylethyl)aminomethyl-2-(2-methylphenyl)benzoyl]methionine lithium salt

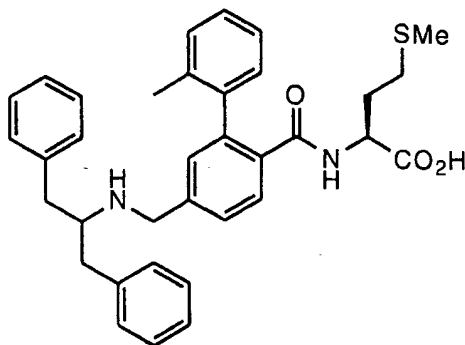
The desired compound was prepared according to the method of Example 158 ¹H NMR (300 MHz, DMSO) δ 1.48-1.75 (m, 2H), 1.75-1.97 (m, 3H), 1.93 (s, 3H), 1.99 (m, 2H), 2.06-2.15 (m, 2H), 2.74-2.87 (m, 4H), 3.65 (brs, 1H), 3.79 (m, 2H), 6.88-6.93 (m, 1H), 6.93 (ddd, $J=6.8, 6.8, 1.0$ Hz, 1H), 7.03 (ddd, $J=6.8, 6.8, 1$ Hz, 1H), 7.10 (d, $J=2.1$ Hz, 1H), 7.10-7.23 (m, 5H), 7.30 (d, $J=8$ Hz, 1H), 7.36 (dd, $J=8$ Hz, 1H), 7.46 (d, $J=7.8$ Hz, 1H), 7.47 (d, $J=7.8$ Hz, 1H). MS (ESI(+)) m/z 516 (M+H)⁺. Anal calcd for C₃₀H₃₂N₃O₃SLi•1.30H₂O: C, 66.11; H, 6.40; N, 7.71. Found: C, 66.15; H, 6.38; N, 7.64.

7810

Example 520

N-[4-N-(2-cyclohexyl-1-ethan-1-ol-2-yl)aminomethyl-2-(2-methylphenyl)benzoyl]methionine lithium salt

7815 The desired compound was prepared according to the method of Example 158 ¹H NMR (300 MHz, DMSO) δ 0.93-1.19 (m, 6H), 1.35-1.77 (m, 4H), 1.77-2.06 (m, 7H), 1.91 (s, 3H), 2.18 (brs, 1H), 2.26 (m, 3H), 3.40-3.48 (m, 1H), 3.59-3.70 (m, 1H), 3.73 (d, $J=14.2$ Hz, 1H), 3.81 (d, $J=13.9$ Hz, 1H), 4.36 (brs, 1H), 6.87-7.00 (m, 1H), 7.11-7.27 (m, 5H), 7.36 (d, $J=8$ Hz, 1H), 7.47 (d, $J=8$ Hz, 1H). MS (ESI(+)) m/z 499 (M+H)⁺. Anal calcd for C₂₈H₃₇N₂O₄SLi•0.75H₂O: C, 64.91; H, 7.49; N, 5.41. Found: C, 64.92; H, 7.39; N, 5.21.

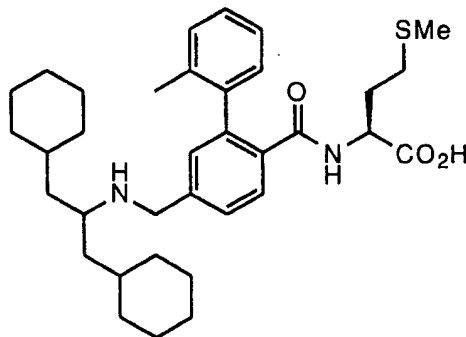


7825

Example 523N-[4-N-(1,3-diphenylpropan-2-yl)aminomethyl-2-(2-methylphenyl)benzoyl]methionine
lithium salt

The desired compound was prepared according to the method of Example 158 ¹H NMR (300 MHz, DMSO) δ 1.48-1.74 (m, 2H), 1.74-2.02 (m, 3H), 1.93 (s, 3H), 2.03-2.14 (m, 2H), 2.54-2.73 (m, 4H), 2.97 (pentet, $J=6.5$ Hz, 1H), 3.63-3.72 (brs, 1H), 3.78 (s, 2H), 6.90 (brs, 2H), 7.05-7.26 (m, 16H), 7.37 (d, $J=7.8$ Hz, 1H). MS (ESI(+)) m/z 567 (M+H)⁺. Anal calcd for C₃₅H₃₇N₂O₃SLi•0.90H₂O: C, 71.38; H, 6.64; N, 4.76. Found: C, 71.40; H, 6.28; N, 4.69.

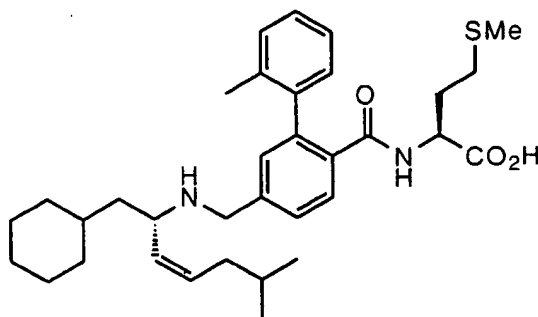
7835

Example 524N-[4-N-(1,3-dicyclohexylpropan-2-yl)aminomethyl-2-(2-methylphenyl)benzoyl]methionine
lithium salt

7840

The desired compound was prepared according to the method of Example 158 ¹H NMR (300 MHz, DMSO) δ 0.70-0.88 (m, 4H), 1.01-1.17 (m, 8H), 1.20-1.38 (m, 4H), 1.46-1.64 (m, 12H), 1.64-1.75 (m, 2H), 1.92 (s, 3H), 1.94-2.02 (m, 2H), 2.13-2.18 (m, 2H), 3.60-3.76 (m, 3H), 6.84-6.97 (m, 1H), 7.04-7.24 (m, 5H), 7.36 (dd, $J=8$, 1 Hz, 1H), 7.45 (d, $J=8$ Hz, 1H). MS (ESI(+)) m/z 579 (M+H)⁺. Anal calcd for

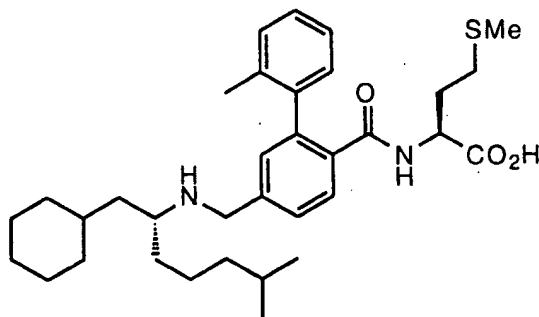
7845 $C_{35}H_{49}N_2O_3SLi \cdot 0.75H_2O$: C, 70.26; H, 8.51; N, 4.68. Found: C, 70.25; H, 8.52; N, 4.57.



7850 Example 526

N-[4-N-(1-Cyclohexyl-6-methylhept-3-en-2-yl)aminomethyl-2-(2-methylphenyl)benzoyl]methionine lithium salt

The desired compound was prepared according to the method of Example 158 1H NMR (300 MHz, DMSO) δ 1.74-0.86 (m, 7H), 1.02-1.19 (m, 4H), 1.27-1.38 (m, 2H), 1.46-1.87 (m, 14H), 1.93 (s, 3H), 1.99 (s, 3H), 2.17 (m, 1H), 3.51-3.82 (m, 3H), 5.11 (m, 1H), 5.43 (m, 1H), 6.83-6.96 (m, 1H), 7.00-7.24 (m, 5H), 7.24-7.36 (m, 1H), 7.47 (d, $J=7$ Hz, 1H). MS (APCI(+)) m/z 565 ($M+H$) $^+$. Anal calcd for $C_{34}H_{47}N_2O_3SLi \cdot 2.02H_2O$: C, 67.20; H, 8.48; N, 4.61. Found: C, 67.24; H, 8.35; N, 4.47.

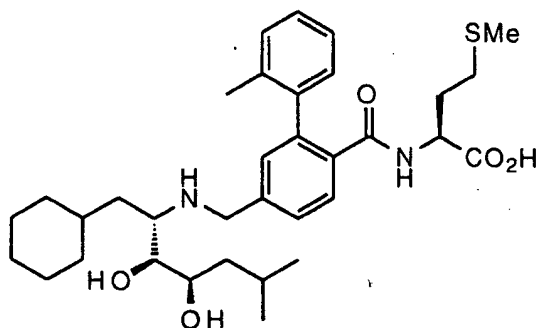


7860 Example 527

N-[4-N-(1-Cyclohexyl-6-methylheptan-2-yl)aminomethyl-2-(2-methylphenyl)benzoyl]methionine lithium salt

The desired compound was prepared according to the method of Example 158 1H NMR (300 MHz, DMSO) δ 0.80 (d, $J=5$ Hz, 3H), 0.82 (d, $J=5$ Hz, 3H), 1.02-1.40 (m, 12H), 1.40-1.65 (m, 12H), 1.75-1.83 (m, 1H), 1.92 (s, 3H), 1.99 (m, 1H), 2.16 (m, 1H),

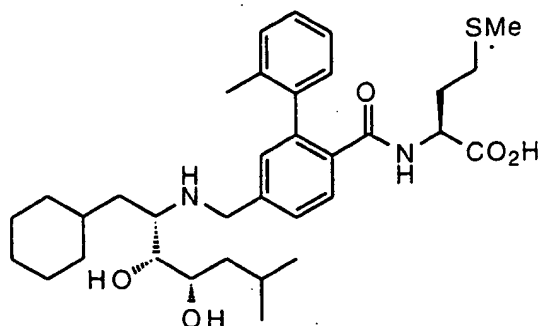
2.43 (m, 1H), 3.60-3.77 (m, 3H), 6.86-6.95 (m, 1H), 7.08-7.22 (m, 5H), 7.35 (d, $J=8.0$ Hz, 1H), 7.47 (d, $J=8.0$ Hz, 1H). MS (APCI(+)) m/z 567 ($M+H$)⁺. Anal calcd for $C_{34}H_{49}N_2O_3SLi \cdot 1.15H_2O$: C, 66.99; H, 8.48; N, 4.60. Found: C, 67.03; H, 8.62; N, 4.49.



Example 528

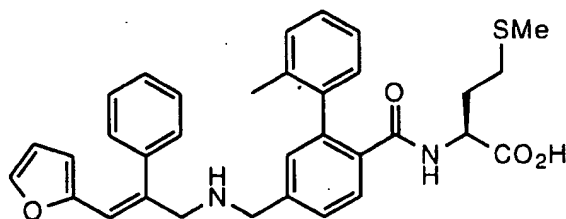
N-[4-N-(1-Cyclohexyl-2,3-dihydroxy-6-methylheptan-2-yl)aminomethyl-2-(2-methylphenyl)benzoyl]methionine

The desired compound was prepared according to the method of Example 158 ¹H NMR (300 MHz, DMSO) δ 0.72-1.35 (m, 10H), 0.85 (d, $J=7$ Hz, 3H), 0.87 (d, $J=7$ Hz, 3H), 1.43-1.76 (m, 6H), 1.82-2.14 (m, 4H), 2.00 (s, 3H), 2.06 (s, 3H), 3.07 (brs, 1H), 3.58 (s, 1H), 3.96-4.14 (m, 2H), 4.40-4.59 (m, 2H), 4.99-5.23 (m, 4H), 6.08-6.10 (m, 1H), 7.17-7.35 (m, 5H), 7.55 (m, 1H), 7.74 (m, 1H), 8.80 (brs, 0.5H), 9.25 (brs, 0.5H). MS (DCI/NH₃) m/z 599 ($M+H$)⁺. Anal. calcd for $C_{34}H_{50}N_2O_5S \cdot 1.55H_2O \cdot 1.05TFA$: C, 55.70; H, 6.90; N, 3.51. Found: C, 55.72; H, 6.91; N, 3.38.

Example 529

7890 N-[4-N-(1-Cyclohexyl-2,3-dihydroxy-6-methylheptan-2-yl)
aminomethyl-2-(2-methylphenyl)benzoyl]methionine

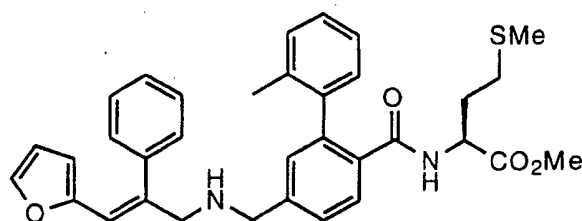
The desired compound was prepared according to the method of Example 158 ¹H NMR (300 MHz, DMSO) δ 0.80-1.40 (m, 16H), 1.45-1.77 (m, 6H), 2.00 (s, 3H), 2.04 (s, 3H), 1.80-2.13 (m, 4H), 3.20-3.40 (m, 1H), 3.59 (m, 1H), 3.39-4.10 (m, 1H), 4.38-4.55 (m, 1H), 4.60-4.90 (m, 4H), 6.10 (m, 1H), 7.20-7.40 (m, 5H), 7.55 (m, 1H), 7.80 (m, 1H), 9.0 (brs, 1H). MS (DCI/NH₃) m/z 599 (M+H)⁺. Anal calcd for C₃₄H₅₀N₂O₅S•1.00H₂O•1.85TFA: C, 54.70; H, 6.56; N, 3.38. Found: C, 54.70; H, 6.59; N, 3.27.

Example 537

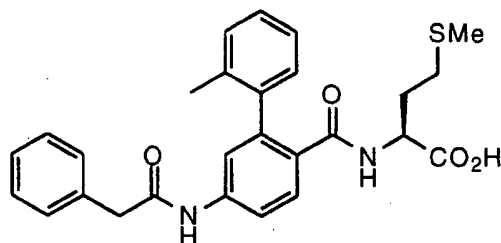
7900 N-[4-(3-furan-2-yl-2-phenylprop-2-en-1-yl)aminomethyl-2-(2-
methylphenyl)benzoyl]methionine lithium salt

7905 The desired compound was prepared according to the method of Examples 158 ¹H NMR (MeOH-*d*₄) δ 7.69-7.61 (m, 1 H), 7.40-7.29 (m, 3 H), 7.22-7.17 (m, 9 H), 6.70 (dd, 1 H, J = 8.7, 2.6 Hz), 6.48 (bs, 1 H), 6.41-6.38 (m, 1 H), 6.15-6.13 (m, 1 H), 5.44 (d, 1 H, J = 3.4 Hz), 4.46-4.38 (m, 1 H), 4.10 (d, 2 H, J = 1.3 Hz), 2.18-1.85 (m, 8 H), 1.79-1.66 (m, 1 H), 1.59-1.52 (m, 1 H); MS m/z 541 (M⁺ + 1, 100).

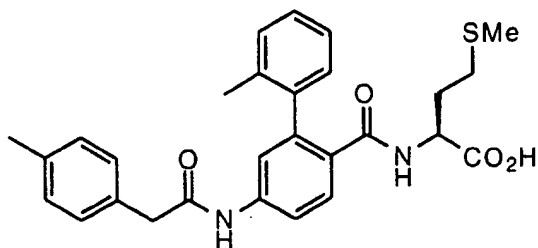
7910

Example 538N-[4-(3-furan-2-yl-2-phenylprop-2-en-1-ylaminomethyl)-2-(2-methylphenyl)benzoyl]methionine methyl ester

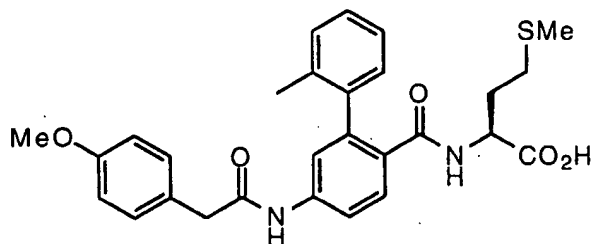
The desired compound was prepared according to the method of Example 158 ¹H NMR (CDCl₃) δ 7.93 (dd, 1 H, *J* = 17.7, 8.6 Hz), 7.42-7.27 (m, 6 H), 7.22-7.19 (m, 4 H), 6.67 (dd, 1 H, *J* = 8.8, 2.4 Hz), 6.52 (bs, 1 H), 6.33 (d, 1 H, *J* = 2.4 Hz), 6.15 (dd, 1 H, *J* = 3.4, 1.7 Hz), 5.70 (t, 1 H, *J* = 8.7 Hz), 5.52 (d, 1 H, *J* = 3.4 Hz), 4.62-4.55 (m, 1 H), 4.30-4.27 (m, 1 H), 4.14-4.11 (m, 2 H), 3.63 (s, 3 H), 2.18-2.00 (m, 8 H), 1.88-1.76 (m, 1 H), 1.56-1.48 (m, 1 H); MS *m/z* 555 (M⁺ + 1, 100).

Example 540N-[4-N-phenylacetyl-amino-2-(2-methylphenyl)benzoyl]methionine lithium salt

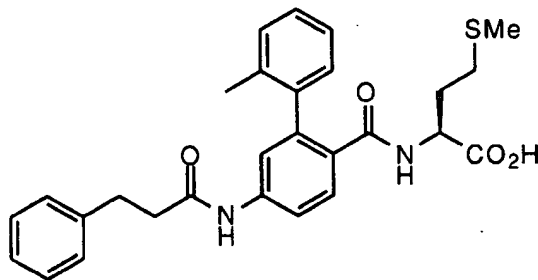
The desired compound was prepared according to the method of Example 57 ¹H NMR (DMSO-*d*₆) δ 10.42 (s, 1 H), 7.60 (d, 1 H, *J* = 8.5 Hz), 7.51 (d, 1 H, *J* = 8.5 Hz), 7.47 (bs, 1 H), 7.34-7.28 (m, 3 H), 7.25-7.16 (m, 6 H), 6.97-6.85 (m, 1 H), 3.68-3.65 (m and s, 3 H total), 2.15-1.85 (m, 8 H), 1.78-1.64 (m, 1 H), 1.59-1.51 (m, 1 H); MS *m/z* 477 (M⁺ + 1, 100).

Example 541N-[4-N-(4'-methylphenylacetyl)amino-2-(2-methylphenyl)benzoyl]methionine lithium salt

The desired compound was prepared according to the method of Example 57 ¹H NMR (DMSO-*d*₆) δ 10.40 (s, 1 H), 7.60 (d, 1 H, *J* = 7.9 Hz), 7.51 (d, 1 H, *J* = 8.5 Hz), 7.46 (bs, 1 H), 7.22-6.83 (m, 9 H), 3.71-3.62 (m, 1 H), 3.60 (s, 2 H), 2.27 (s, 3 H), 2.23-1.86 (m, 8 H), 1.71-1.64 (m, 1 H), 1.60-1.52 (m, 1 H); MS *m/z* 491 (*M*⁺ + 1, 100).

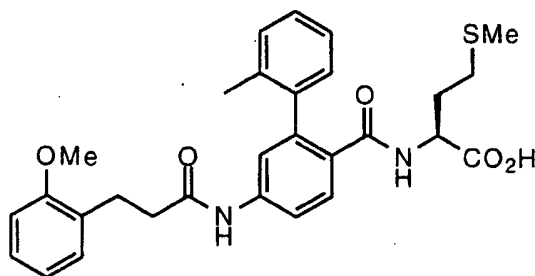
Example 542N-[4-N-(4'-methoxyphenylacetyl)amino-2-(2-methylphenyl)benzoyl]methionine lithium salt

The desired compound was prepared according to the method of Example 57 ¹H NMR (DMSO-*d*₆) δ 7.67-7.63 (m, 2 H), 7.50-7.45 (m, 1 H), 7.26-7.09 (m, 6 H), 6.89-6.85 (m, 2 H), 6.81-6.77 (m, 1 H), 4.24-4.20 (m, 1 H), 3.77 and 3.74 (2s, 3 H total), 3.62 and 3.39 (2s, 2 H total), 2.23-1.95 (m, 8 H), 1.89-1.78 (m, 1 H), 1.66-1.59 (m, 1 H); MS *m/z* 507 (*M*⁺ + 1, 100).

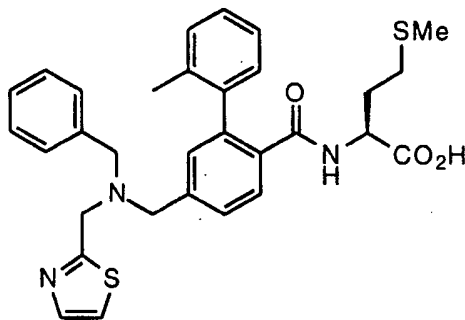
Example 543

7955 N-[4-N-(3-phenylpropionoyl)amino-2-(2-methylphenyl)benzoyl]methionine lithium salt

The desired compound was prepared according to the method of Example 57 ¹H NMR (DMSO-*d*₆) δ 10.17 (bs, 1 H), 7.60 (d, 1 H, *J* = 7.9 Hz), 7.51 (d, 1 H, *J* = 8.6 Hz), 7.45 (bs, 1 H), 7.29-6.85 (m, 10 H), 3.71-3.65 (m, 1 H), 2.90 and 2.69 (2t, 2 H total, *J* = 7.9 Hz), 2.64 and 2.15 (2t, 2 H total, *J* = 7.9 Hz), 2.17-1.83 (m, 8 H), 1.71-1.64 (m, 1 H), 1.59-1.53 (m, 1 H); MS *m/z* 491 (*M*⁺ + 1, 100).

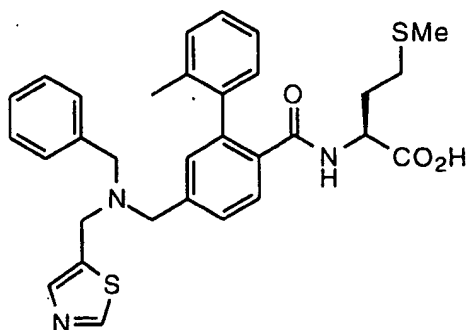
Example 5447965 N-[4-N-(3-(2-methoxyphenyl)propionoyl)amino-2-(2-methylphenyl)benzoyl]methionine lithium salt

The desired compound was prepared according to the method of Example 57 ¹H NMR (DMSO-*d*₆) δ 10.10 (bs, 1 H), 7.59 (d, 1 H, *J* = 7.9 Hz), 7.50 (d, 1 H, *J* = 8.6 Hz), 7.45 (bs, 1 H), 7.22-7.09 (m, 6 H), 6.96 (d, 1 H, *J* = 7.9 Hz), 6.89-6.79 (m, 3 H), 3.78 and 3.76 (2s, 3 H total), 2.86 and 2.69 (2t, 2 H total, *J* = 7.9 Hz), 2.59 and 2.07 (2t, 2 H total, *J* = 7.9 Hz), 2.17-1.84 (m, 8 H), 2.71-2.63 (m, 1 H), 1.58-1.53 (m, 1 H); MS *m/z* 521 (*M*⁺ + 1, 100).

Example 5487975 N-[4-N-benzyl-N-(thiazol-2-ylmethyl)aminomethyl-2-(2-methylphenyl)benzoyl]methionine

The desired compound was prepared according to the method of Example 158 ¹H nmr (300 MHz, DMSO *d*₆): δ 8.09, d, 1H; 7.72, d, 1H; 7.66, d, 1H; 7.50, m, 2H; 7.38,

7980 m, 4H; 7.23, m, 4H; 7.14, m, 2H; 4.20, ddd, 1H; 3.89, s, 2H; 3.70, s, 2H; 3.68, s, 2H; 2.09, m, 4H; 1.96, s, 3H; 1.63 - 1.90, m, 2H. MS (APCI(+)) 560 (MH⁺). Calc'd for C₃₁H₃₃N₃O₃S₂•0.32 H₂O: C 65.84, H 6.00, N 7.43: Found: C 65.85, H 5.75, N 7.34



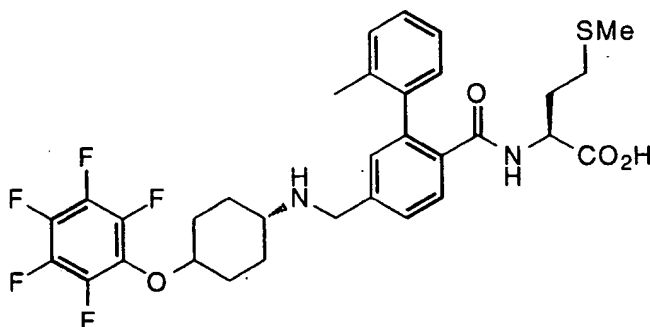
7985

Example 549

N-[4-N-benzyl-N-(thiazol-5-ylmethyl)aminomethyl-2-(2-methylphenyl)benzoyl]methionine

The desired compound was prepared according to the method of Example 158 ¹H nmr (300 MHz, DMSO d₆): δ 12.45, bs, 1H; 9.03, s, 1H; 8.12, d, 1H; 7.79, s, 1H; 7.48, dd, 2H; 7.35, m, 4H; 7.04 - 7.28, m, 6H; 4.21, ddd, 1H; 3.81, s, 2H; 3.61, s, 2H; 3.58, s, 1H; 1.98 - 2.21, 5H; 1.96, s, 3H; 1.61 - 1.89, m, 2H. MS (APCI(+)) 560 (MH⁺). Calc'd for C₃₁H₃₃N₃O₃S₂•0.78 H₂O: C 64.89, H 6.07, N 7.32: Found: C 64.89, H 5.71, N 7.29

7995

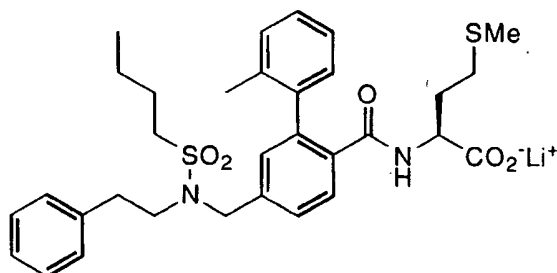


Example 596

N-[4-N-(4-trans-pentafluorophenoxy)cyclohexylaminomethyl-2-(2-methylphenyl)benzoyl]methionine

8000 A solution of *trans*-4-aminocyclohexanol (3.03 g, 20.0 mmol) and diisopropylethylamine (7.4 mL, 42.0 mmol) in methylene chloride (30 mL) was treated with *t*-butyl dicarbonate (4.37 g, 20.0 mmol) over 5 minutes. The reaction stirred overnight at room temperature and was washed with 1 M HCl, 5% NaHCO₃, and brine to give the Boc-

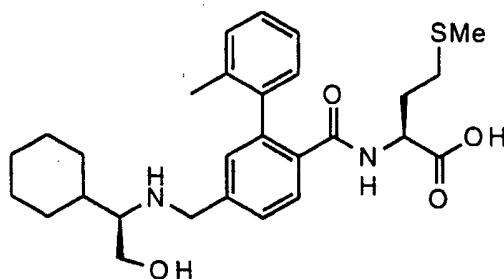
amine in nearly quantitative yield. A portion of this product (215 mg, 1.0 mmol) was
 8005 combined with hexafluorobenzene (223 mg, 1.2 mmol) and 15-crown-5 (44 mg, 0.2 mmol)
 in DMF (3 mL) at room temperature. NaH (60% in oil, 4.4 mg, 1.2 mmol) was added and
 stirred overnight. Standard aqueous workup provided 149 mg of the protected
 pentafluorophenyl ether which was treated with excess TFA in methylene chloride, stripped
 to dryness, and reductively alkylated and saponified in a manner analogous to Example 158
 8010 to provide 160 mg of the title compound. MS m/e 635 ($M-H$)⁻. ¹H NMR (CDCl₃, 300
 MHz) δ 1.5 (m, 4H), 1.79 (m, 1H), 2.05 (m, 12H), 2.81 (m, 1H), 4.05 (m, 4H), 6.25 (m,
 1H), 6.81 (m, 2H), 7.1-7.7 (m, 7H).



Example 598

N-[4-(N-2-phenethyl-N-butanefonylaminomethyl)-2-(2-methylphenyl)benzoyl]methionine

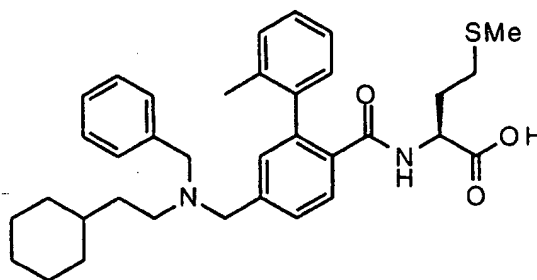
The desired compound was prepared according to the method of Example 157. ¹H
 8020 (300MHz, DMSO-d₆, δ) 7.62 (1H, d, J=7Hz), 7.52 (1H, dd, J=7&2Hz), 7.20-7.10 (10H,
 m), 7.14 (1H, bd, J=7Hz), 4.65 (2H, bs), 3.76 (1H, m), 3.00 (2H, m), 2.78 (2H, m),
 2.25-2.00 (5H, m), 1.99 (3H, s), 1.90-1.70 (4H, m), 1.62 (2H, m), 1.37 (2H, m), 0.92
 (3H, t, J=8Hz). m/e (ESI) 595 (MH)⁺ Anal. calc. for C₃₂H₃₉LiN₂O₅S₂·0.50 H₂O C
 8025 62.83, H 6.59, N 4.38 Found C 62.59, H 6.59, N 4.44



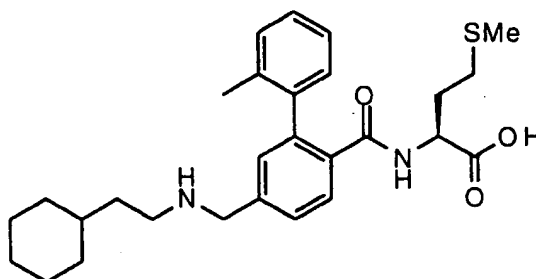
Example 604

N-[4-(2-cyclohexylethan-1-yl-2-ylaminomethyl)-2-(2-methylphenyl)benzoyl]methionineLithium Salt

The desired compound was prepared according to the method of Example 158. ¹H NMR (DMSO-d₆, 300 MHz) δ 7.48 (d, J=8 Hz, 1H), 7.37 (dd, J=8, 1 Hz, 1H), 7.20-7.08 (m, 4H), 6.90 (m, 1H), 4.40 (t, J=5 Hz, 1H), 3.82-3.65 (m, 3H), 3.46 (m, 1H), 3.31 (m, 1H), 2.28-2.12 (m, 2H), 2.02-1.80 (m, 7H), 1.77-1.37 (m, 8H), 1.18-0.92 (m, 5H); Anal. Calcd for C₂₈H₃₇LiN₂O₄S•1.35 H₂O: C, 63.58; H, 7.57; N, 5.30. Found: C, 63.55; H, 7.31; N, 4.89.

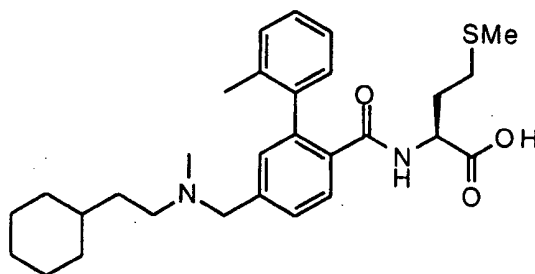
Example 605N-[4-(N-benzyl-N-(2-cyclohexylethyl)aminomethyl)-2-(2-methylphenyl)benzoyl]methionineLithium Salt

The desired compound was prepared according to the method of Example 158. MS (CI/NH₃) m/z: (M-H)⁻ 571; ¹H NMR (DMSO-d₆, 300 MHz) δ 7.50 (d, J=8 Hz, 1H), 7.38-7.12 (m, 10H), 6.92 (d, J=6 Hz, 1H), 3.69 (m, 1H), 3.56 (s, 2H), 3.53 (s, 2H), 2.38 (t, J=7 Hz, 2H), 2.15-1.95 (m, 4H), 1.91 (s, 3H), 1.58-1.42 (m, 7H), 1.38-1.02 (m, 7H), 0.81-0.68 (m, 2H); Anal. Calcd for C₃₅H₄₃LiN₂O₃S•1.75 H₂O: C, 68.89; H, 7.68; N, 4.59. Found: C, 68.85; H, 7.44; N, 4.37.

Example 607

N-[4-(N-2-cyclohexylethylaminomethyl)-2-(2-methylphenyl)benzoyl]methionineTrifluoroacetate Salt

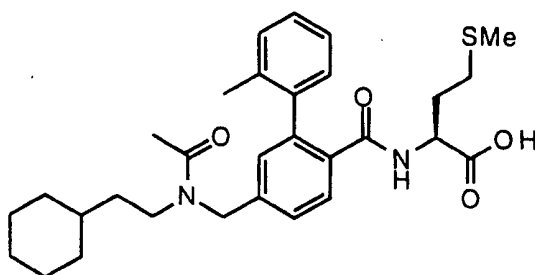
8055 The desired compound was prepared according to the method of Example 158. MS (CI/NH₃) m/z: (M+H)⁺ 483; ¹H NMR (DMSO-d₆, 300 MHz) δ 8.09 (m, 1H), 7.49-7.42 (m, 2H), 7.26 (m, 1H), 7.16-6.98 (m, 3H), 4.14 (m, 1H), 4.11 (s, 2H), 2.87-2.80 (m, 2H), 2.11-1.90 (m, 5H), 1.86 (s, 3H), 1.78-1.47 (m, 7H), 1.45-1.37 (m, 2H), 1.26-1.00 (m, 4H), 0.87-0.72 (m, 2H); Anal. Calcd for C₂₈H₃₈N₂O₃S•C₂HF₃O₂•1.45 H₂O: C, 57.76; H, 6.93; N, 4.49. Found: C, 57.69; H, 6.51; N, 4.48.

Example 608

8065 N-[4-(N-(2-cyclohexylethyl)-N-methylaminomethyl)-2-(2-methylphenyl)benzoyl]methionine

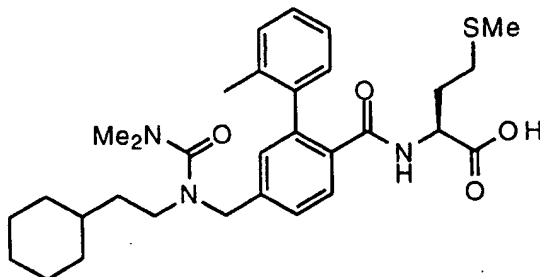
Lithium Salt

The desired compound was prepared according to the method of Example 158. MS (CI/NH₃) m/z: (M+H)⁺ 497; ¹H NMR (DMSO-d₆, 300 MHz) δ 7.49 (d, J=8 Hz, 1H), 7.32 (dd, J=8, 1 Hz, 1H), 7.25-7.06 (m, 4H), 6.93 (d, J=6 Hz, 1H), 3.73-3.64 (m, 1H), 3.49 (s, 2H), 2.32 (t, J=7 Hz, 2H), 2.15 (m, 1H), 2.12 (s, 3H), 2.06-1.80 (m, 3H), 1.92 (s, 3H), 1.74-1.50 (m, 7H), 1.35-1.05 (m, 7H), 0.90-0.76 (m, 2H); Anal. Calcd for C₂₉H₃₉LiN₂O₃S•1.05 H₂O: C, 66.78; H, 7.94; N, 5.37. Found: C, 66.81; H, 7.75; N, 5.07.

Example 609

N-[4-(N-acetyl-N-(2-cyclohexylethyl)aminomethyl)-2-(2-methylphenyl)benzoyl]methionine
Lithium Salt

8080 The desired compound was prepared according to the method of Example 607. The resultant amine was reacted with acetic anhydride - lithium carbonate under Schotten-Baumann conditions. MS (CI/NH₃) m/z: (M-H)⁻ 523; ¹H NMR (DMSO-d₆, 300 MHz) δ 7.59 (minor conformer) 7.53 (major conformer) (d, J=8 Hz, 1H), 7.31 (d, J=8 Hz, 1H), 7.25-7.14 (m, 3H), 7.07-6.96 (m, 2H), 4.63 (minor conformer) 4.57 (major conformer) (s, 2H), 3.80 (m, 1H), 3.33-3.25 (m, 2H), 2.21-1.85 (m, 10H), 1.77-1.56 (m, 7H), 1.44-1.30 (m, 3H), 1.25-1.07 (m, 4H), 0.95-0.83 (m, 2H); Anal. Calcd for C₃₀H₃₉LiN₂O₄S•1.45 H₂O: C, 64.72; H, 7.59; N, 5.03. Found: C, 64.75; H, 7.40; N, 4.71.



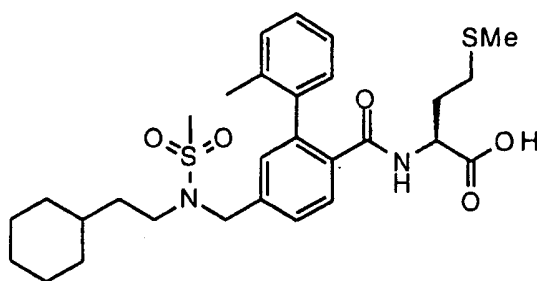
8090

Example 610

N-[4-(N-(N,N-dimethylaminocarbonyl)-N-(2-cyclohexylethyl)aminomethyl)-2-(2-methylphenyl)benzoyl]methionine

8095 The compound resulting from Example 607 was treated with dimethyl carbamoyl chloride under Schotten-Baumann conditions to yield the title compound. MS (CI/NH₃) m/z: (M+H)⁺ 554; ¹H NMR (DMSO-d₆, 300 MHz) δ 8.18 (d, J=8 Hz, 1H), 7.54 (d, J=8 Hz, 1H), 7.38 (dd, J=8, 2 Hz, 1H), 7.29-7.13 (m, 4H), 4.40 (s, 2H), 4.28 (m, 1H), 3.13-3.06 (m, 2H), 2.80 (s, 6H), 2.29-2.06 (m, 5H), 2.02 (m, 3H), 1.94-1.62 (m, 6H), 1.47-1.15 (m, 7H), 0.96-0.84 (m, 2H); Anal. Calcd for C₃₁H₄₃N₃O₄S•0.45 H₂O: C, 66.27; H, 7.88; N, 7.48. Found: C, 66.37; H, 8.10; N, 6.88.

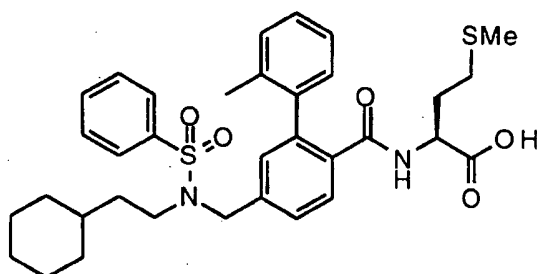
8100

Example 611

8105 N-[4-(N-(2-cyclohexylethyl)-N-methanesulfonylaminomethyl)-2-(2-methylphenyl)benzoyl]methionine Lithium Salt

The compound resulting from Example 607 was treated with methanesulfonyl chloride under Schotten-Baumann conditions to yield the title compound. MS (CI/NH₃) m/z: (M-H)⁻ 559; ¹H NMR (DMSO-d₆, 300 MHz) δ 7.54 (d, J=8 Hz, 1H), 7.41 (d, J=8 Hz, 1H), 7.25-7.13 (m, 4H), 6.97 (d, J=7 Hz, 1H), 4.36 (s, 2H), 3.67 (m, 1H), 3.17-3.12 (m, 2H), 2.96 (s, 3H), 2.17-1.91 (m, 6H), 1.70-1.48 (m, 9H), 1.31-1.04 (m, 6H), 0.82-0.69 (m, 2H); Anal. Calcd for C₂₉H₃₉LiN₂O₅S₂•2.75 H₂O: C, 56.52; H, 7.28; N, 4.55. Found: C, 56.72; H, 6.49; N, 3.92.

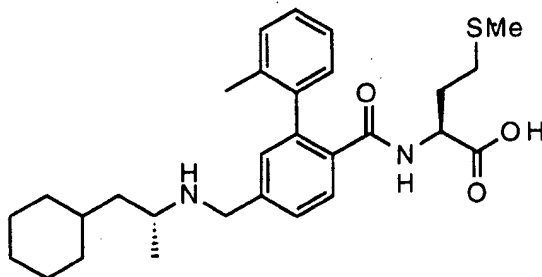
8115

Example 612

N-[4-(N-benzenesulfonyl-N-(2-cyclohexylethyl)aminomethyl)-2-(2-methylphenyl)benzoyl]methionine Lithium Salt

8120 The compound resulting from Example 607 was treated with benzenesulfonyl chloride under Schotten-Baumann conditions to yield the title compound. MS (CI/NH₃) m/z: (M-H)⁻ 621; ¹H NMR (DMSO-d₆, 300 MHz) δ 7.86 (m, 1H), 7.72-7.59 (m, 4H), 7.51 (d, J=8 Hz, 1H), 7.36 (m, 1H), 7.26-7.07 (m, 4H), 6.96 (d, J=6 Hz, 1H), 4.36 (s, 2H), 3.66 (m, 1H), 3.10 (m, 2H), 2.16-1.92 (m, 5H), 1.70-1.40 (m, 7H), 1.30-0.99 (m, 6H), 0.90-0.61 (m, 5H); Anal. Calcd for C₃₄H₄₁LiN₂O₅S₂•1.25 H₂O: C, 62.70; H, 6.73; N, 4.30. Found: 63.10; H, 6.72; N, 3.52.

8125

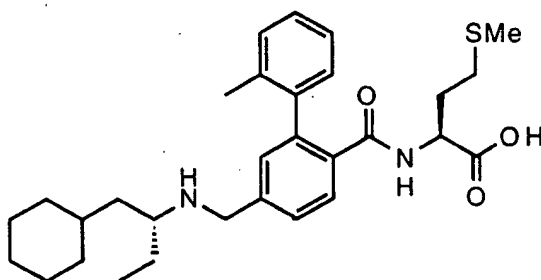


8130

Example 613N-[4-(3-cyclohexylpropan-2-ylaminomethyl)-2-(2-methylphenyl)benzoyl]methionine

The desired compound was prepared according to the method of Example 158 MS (CI/NH₃) m/z: (M+H)⁺ 497; ¹H NMR (DMSO-d₆, 300 MHz) δ 7.63 (m, 1H), 7.52-7.43 (m, 2H), 7.25-7.04 (m, 4H), 4.06 (m, 1H), 3.97 (d, J=14 Hz, 1H), 3.89 (d, J=14 Hz, 1H), 2.85 (m, 1H), 2.17-1.94 (m, 5H), 1.94 (s, 3H), 1.84-1.52 (m, 7H), 1.50-1.02 (m, 9H), 0.90-0.77 (m, 2H); Anal. Calcd for C₂₉H₄₀N₂O₃S•1.55 H₂O: C, 66.39; H, 8.28; N, 5.34. Found: 66.39; H, 7.89; N, 5.11.

8135

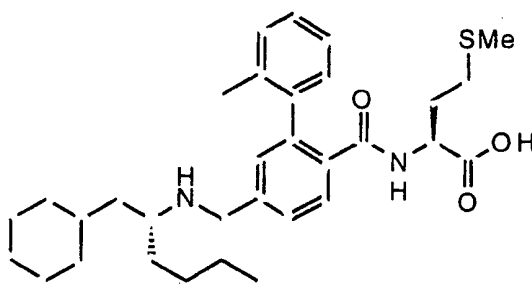


8140

Example 614N-[4-(4-cyclohexylbutan-3-ylaminomethyl)-2-(2-methylphenyl)benzoyl]methionine LithiumSalt

The desired compound was prepared according to the method of Example 158 MS (CI/NH₃) m/z: (M+H)⁺ 511; ¹H NMR (DMSO-d₆, 300 MHz) δ 7.48 (d, J=8 Hz, 1H), 7.36 (d, J=6 Hz, 1H), 7.25-7.09 (m, 4H), 7.00-6.85 (m, 1H), 3.80-3.65 (m, 3H), 2.42 (m, 1H), 2.20-1.50 (m, 15H), 1.41-1.06 (m, 8H), 0.90-0.70 (m, 2H), 0.79 (t, J=7 Hz, 3H); Anal. Calcd for C₃₀H₄₁LiN₂O₃S•1.25 H₂O: C, 66.83; H, 8.13; N, 5.20. Found: 66.86; H, 7.91; N, 4.93.

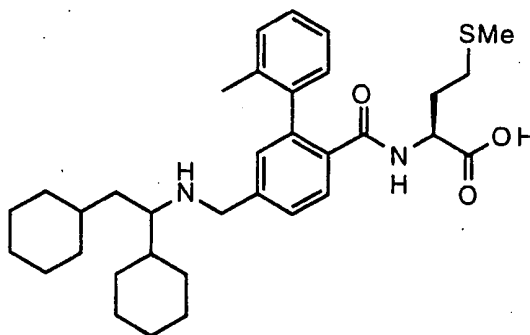
8150

Example 615N-[4-(6-cyclohexylhexan-5-ylaminomethyl)-2-(2-methylphenyl)benzoyl]methionine Lithium Salt

8155

The desired compound was prepared according to the method of Example 158 MS (CI/NH₃) m/z: (M-H)⁻ 537; ¹H NMR (DMSO-d₆, 300 MHz) δ 7.47 (d, J=8 Hz, 1H), 7.36 (dd, J=8, 1 Hz, 1H), 7.24-7.07 (m, 4H), 6.90 (m, 1H), 3.75-3.62 (m, 3H), 2.45 (m, 1H), 2.18-1.50 (m, 15H), 1.40-1.07 (m, 12H), 0.88-0.75 (m, 5H); Anal. Calcd for C₃₂H₄₅LiN₂O₃S•1.05 H₂O: C, 68.19; H, 8.42; N, 4.97. Found: 68.19; H, 8.25; N, 4.77.

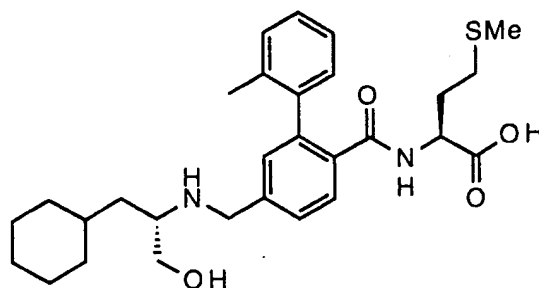
8160

Example 616N-[4-(1,2-dicyclohexylethylaminomethyl)-2-(2-methylphenyl)benzoyl]methionine Lithium Salt

8165

The desired compound was prepared according to the method of Example 158 MS (CI/NH₃) m/z: (M+H)⁺ 565; ¹H NMR (DMSO-d₆, 300 MHz) δ 7.47 (d, J=8 Hz, 1H), 7.36 (m, 1H), 7.23-7.12 (m, 4H), 6.91 (m, 1H), 3.77-3.63 (m, 3H), 2.30 (m, 1H), 2.15 (m, 1H), 2.03-1.85 (m, 6H), 1.80-1.40 (m, 12H), 1.30-0.65 (m, 15H); Anal. Calcd for C₃₄H₄₇LiN₂O₃S•2.25 MeOH: C, 67.05; H, 8.15; N, 4.60. Found: 67.37; H, 7.69; N, 4.46.

8170

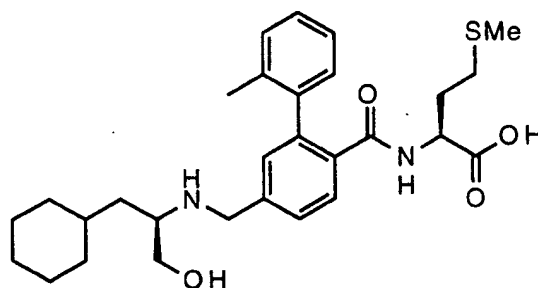


8175

Example 617N-[4-(3-cyclohexylpropan-1-ol-2-ylaminomethyl)-2-(2-methylphenyl)benzoyl]methionine

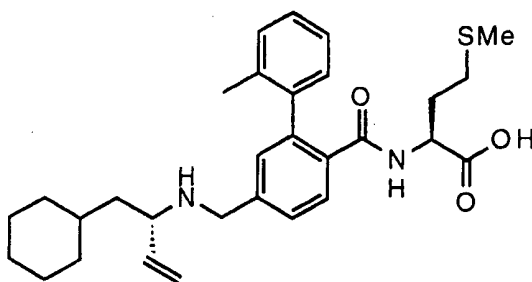
The desired compound was prepared according to the method of Example 158 MS (Cl/NH₃) m/z: (M+H)⁺ 513; ¹H NMR (DMSO-d₆, 300 MHz) δ 7.85 (m, 1H), 7.49 (d, J=7 Hz, 1H), 7.42 (d, J=7 Hz, 1H), 7.23-7.05 (m, 4H), 4.18-4.12 (m, 2H), 3.92-3.84 (m, 2H), 3.45 (m, 1H), 2.65 (m, 1H), 2.18-2.00 (m, 4H), 1.85-1.55 (m, 6H), 1.38-1.08 (m, 10 H), 0.89-0.77 (m, 3H); Anal. Calcd for C₂₉H₄₀N₂O₄S•1.65 H₂O: C, 64.21; H, 8.05; N, 5.16. Found: 64.26; H, 7.64; N, 4.77.

8185

Example 618N-[4-(3-cyclohexylpropan-1-ol-2-ylaminomethyl)-2-(2-methylphenyl)benzoyl]methionineTrifluoroacetate Salt

The desired compound was prepared according to the method of Example 158 MS (Cl/NH₃) m/z: (M+H)⁺ 513; ¹H NMR (DMSO-d₆, 300 MHz) δ 7.85 (m, 1H), 7.49 (d, J=7 Hz, 1H), 7.42 (d, J=7 Hz, 1H), 7.23-7.05 (m, 4H), 4.18-4.12 (m, 2H), 3.92-3.84 (m, 2H), 3.45 (m, 1H), 2.65 (m, 1H), 2.18-2.00 (m, 4H), 1.85-1.55 (m, 6H), 1.38-1.08 (m, 10 H), 0.89-0.77 (m, 3H); Anal. Calcd for C₂₉H₄₀N₂O₄S•C₂HF₃O₂•1.70 H₂O: C, 56.64; H, 6.81; N, 4.26. Found: 56.67; H, 6.89; N, 4.11.

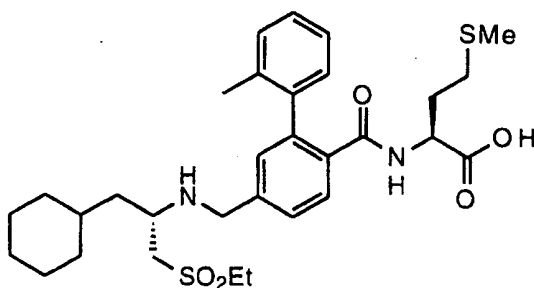
8195

Example 619

8200 N-[4-(2-cyclohexylprop-1-en-2-ylaminomethyl)-2-(2-methylphenyl)benzoyl]methionine
Lithium Salt

The desired compound was prepared according to the method of Example 158 MS (CI/NH₃) m/z: (M-H)⁻ 507; ¹H NMR (DMSO-d₆, 300 MHz) δ 7.47 (d, J=8 Hz, 1H), 7.32 (m, 1H), 7.25-7.07 (m, 4H), 6.93 (m, 1H), 5.52 (ddd, J=17, 10, 8 Hz, 1H), 5.05 (dd, J=10, 2 Hz, 1H), 4.97 (dd, J=17, 2 Hz, 1H), 3.77 (d, J=15 Hz, 1H), 3.70 (m, 1H), 3.57 (d, J=15 Hz, 1H), 2.94 (m, 1H), 2.17-1.50 (m, 15H), 1.38-1.06 (m, 6H), 0.90-0.77 (m, 2H); Anal. Calcd for C₃₀H₃₉LiN₂O₃S•1.90 H₂O: C, 65.65; H, 7.86; N, 5.10. Found: 65.64; H, 7.34; N, 4.80.

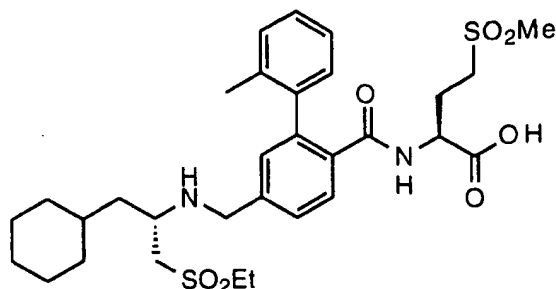
8210

Example 620

N-[4-(3-cyclohexyl-1-ethylsulfonylpropan-2-ylaminomethyl)-2-(2-methylphenyl)benzoyl]methionine Lithium Salt

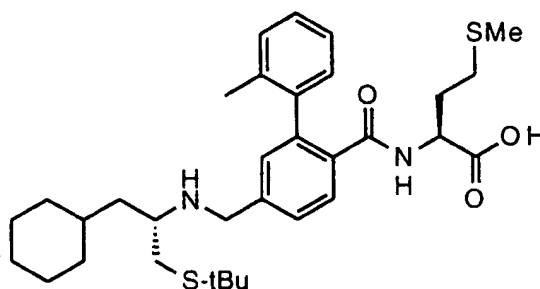
8215 The desired compound was prepared according to the method of Example 158 MS (CI/NH₃) m/z: (M+H)⁺ 589; ¹H NMR (DMSO-d₆, 300 MHz) δ 7.52 (d, J=8 Hz, 1H), 7.38 (dd, J=8, 1 Hz, 1H), 7.27-7.10 (m, 4H), 6.97 (m, 1H), 3.83-3.68 (m, 3H), 3.33 (m, 1H), 3.20-3.07 (m, 3H), 2.97 (dd, J=14, 5 Hz, 1H), 2.28-1.81 (m, 8H), 1.78-1.08 (m, 16H), 0.92-0.75 (m, 2H); Anal. Calcd for C₃₁H₄₃LiN₂O₅S₂•4.25 H₂O: C, 55.46; H, 7.73; N, 4.17. Found: 55.43; H, 6.94; N, 4.03.

8220

Example 621

8225 N-[4-(3-cyclohexyl-1-ethylsulfonylpropan-2-ylaminomethyl)-2-(2-methylphenyl)benzoyl]-2-
amino-4-methanesulfonylbutanoic acid Lithium Salt

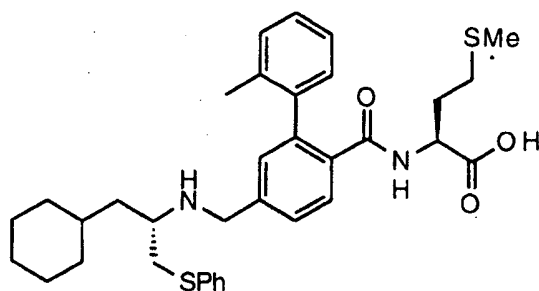
The desired compound was prepared according to the method of Example 158 MS (CI/NH₃) m/z: (M-H)⁻619; ¹H NMR (DMSO-d₆, 300 MHz) δ 7.53 (d, J=8 Hz, 1H), 7.37 (d, J=8 Hz, 1H), 7.25-7.09 (m, 4H), 6.97 (m, 1H), 3.78-3.65 (m, 3H), 3.25 (m, 1H),
 8230 3.21-2.91 (m, 4H), 2.80 (s, 3H), 2.28-1.07 (m, 21H), 0.92-0.84 (m, 2H); Anal. Calcd for C₃₁H₄₃LiN₂O₇S₂•1.25 H₂O: C, 57.35; H, 7.06; N, 4.31. Found: 57.35; H, 7.03; N, 4.11.

Example 622

8235 N-[4-(3-cyclohexyl-1-t-butylthiopropyl-2-ylaminomethyl)-2-(2-
methylphenyl)benzoyl]methionine Lithium Salt

The desired compound was prepared according to the method of Example 158 MS (CI/NH₃) m/z: (M+H)⁺584; ¹H NMR (DMSO-d₆, 300 MHz) δ 7.747 (d, J=8 Hz, 1H), 7.37 (dd, J=8, 1 Hz, 1H), 7.23-7.13 (m, 4H), 6.97 (m, 1H), 3.87-3.72 (m, 2H), 3.65 (m, 1H), 2.63 (m, 1H), 2.18-1.77 (m, 8H), 1.74-1.00 (m, 24 H), 0.91-0.68 (m, 2H); Anal. Calcd for C₃₃H₄₇LiN₂O₃S₂•4.50 EtOH: C, 59.39; H, 7.78; N, 4.70. Found: 59.65; H, 7.43; N, 3.91.

8245

Example 623

N-[4-(3-cyclohexyl-1-phenylthiopropyl)-2-aminomethyl]benzoyl-L-methionine Lithium Salt


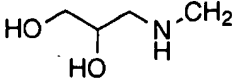
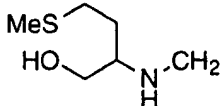
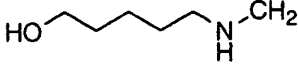
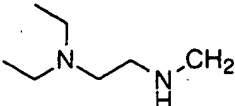
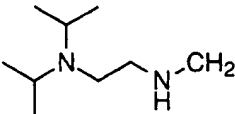
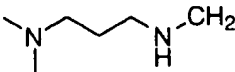
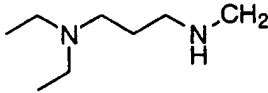
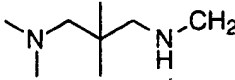
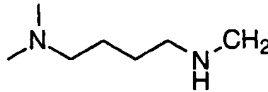
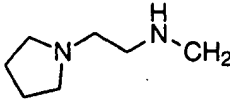
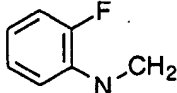
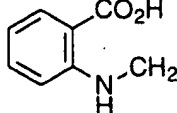
The desired compound was prepared according to the method of Example 158 MS (CI/NH₃) m/z: (M+H)⁺605; ¹H NMR (DMSO-d₆, 300 MHz) δ 7.7.46 (d, J=8 Hz, 1H), 7.34-6.85 (m, 11H), 3.86-3.65 (m, 3H), 3.11 (dd, J=13, 5 Hz, 1H), 2.87 (m, 1H), 2.67 (m, 1H), 2.17-0.60 (m, 23H); Anal. Calcd for C₃₅H₄₃LiN₂O₃S₂•1.20 H₂O: C, 66.47; H, 7.24; N, 4.43. Found: 66.43; H, 7.27; N, 4.49.

Examples 626-668 and Examples 669-758

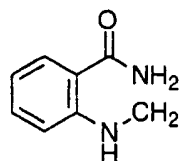
Compounds 626-667, 669-722, and 723-727 were synthesized by reductive amination of the compound described in Example 625, by the procedure described in Example 158

R₁ = Ph

<u>Example</u>	<u>R₃L₁</u>	<u>MS (M+H)⁺</u>
626		419
627		475
628		417
629		431
630		445

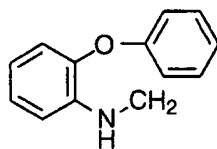
631		417
632		433
633		477
634		445
635		458
636		486
637		444
638		472
639		472
640		458
641		456
642		453
643		479

644



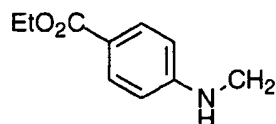
478

645



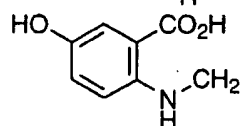
527

646



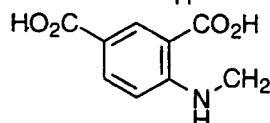
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647



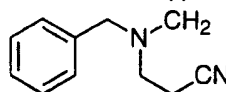
495

648



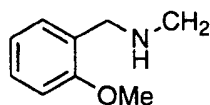
459

649



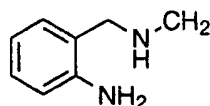
502

650



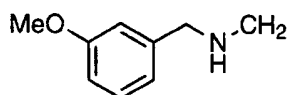
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651



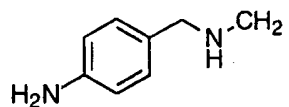
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652



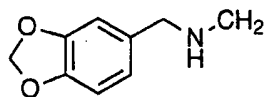
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653



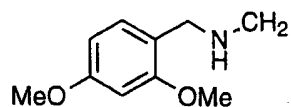
464

654



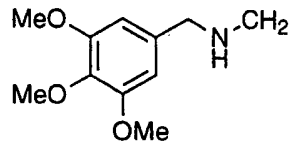
493

655

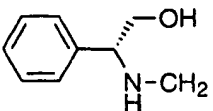
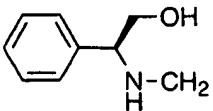
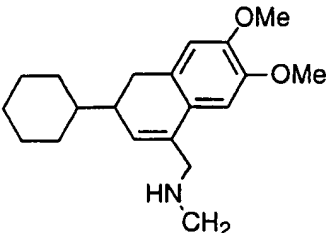
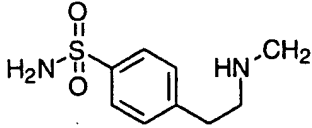
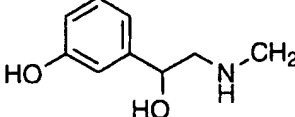
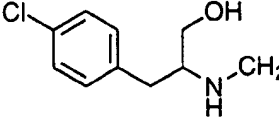
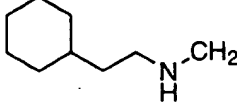
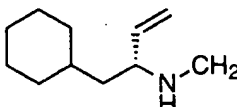
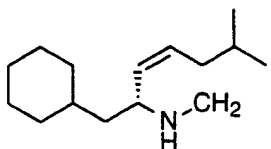
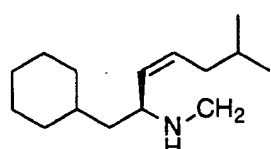
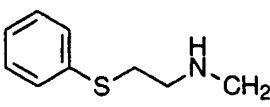


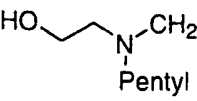
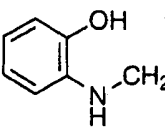
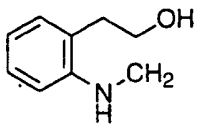
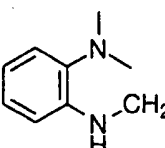
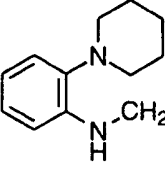
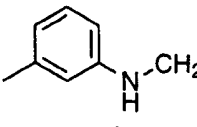
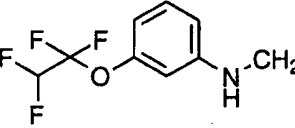
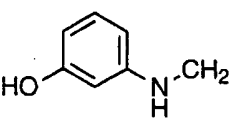
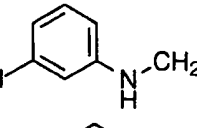
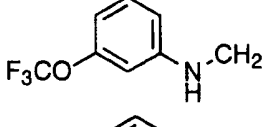
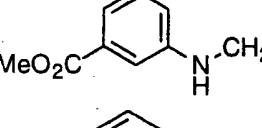
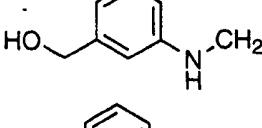
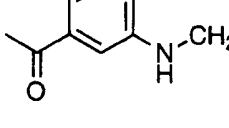
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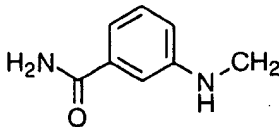
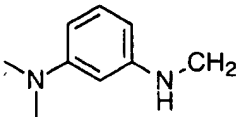
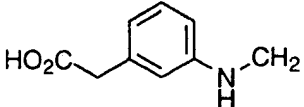
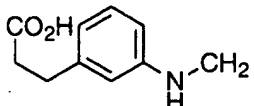
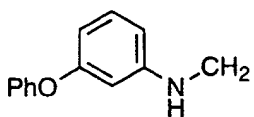
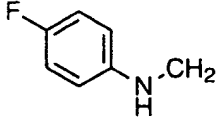
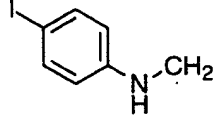
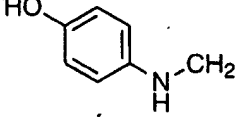
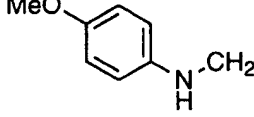
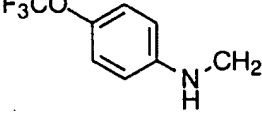
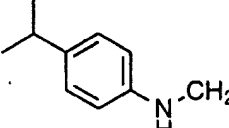
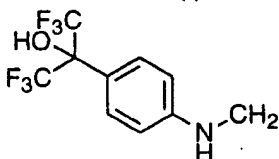
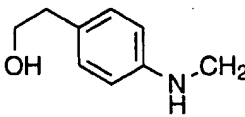
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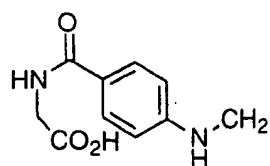
539

657		479
658		479
659		643
660		542
661		495
662		527
663		469
664		495
665		551
666		551
667		495

669	 <chem>CCCCCNCCO</chem>	457
670	 <chem>c1ccccc1NCc2ccccc2</chem>	435
671	 <chem>c1ccccc1NCCO</chem>	479
672	 <chem>CN(Cc1ccccc1)c2ccccc2</chem>	478
673	 <chem>c1ccccc1NC2CCCC2</chem>	518
674	 <chem>Cc1cccc(c1)NCc2ccccc2</chem>	449
675	 <chem>COc1ccc(NC2=CC=CC=C2)cc1C(F)(F)F</chem>	551
676	 <chem>Oc1cccc(NC2=CC=CC=C2)c1</chem>	451
677	 <chem>Ic1cccc(NC2=CC=CC=C2)c1</chem>	561
678	 <chem>COc1ccc(NC2=CC=CC=C2)cc1C(F)(F)F</chem>	519
679	 <chem>COc1ccc(NC2=CC=CC=C2)cc1</chem>	493
680	 <chem>OCCc1ccc(NC2=CC=CC=C2)cc1</chem>	465
681	 <chem>CC(=O)c1ccc(NC2=CC=CC=C2)cc1</chem>	477

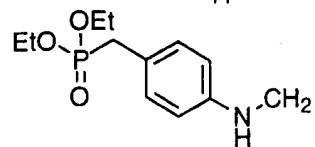
682		478
683		478
684		493
685		507
686		527
687		453
688		561
689		451
690		465
691		519
692		477
693		601
694		479

695



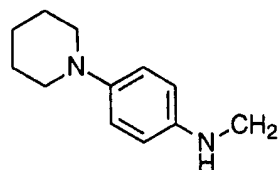
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696



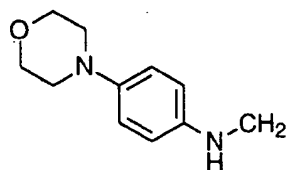
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697



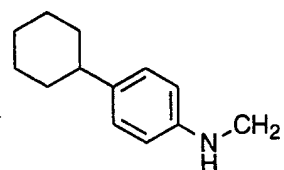
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698



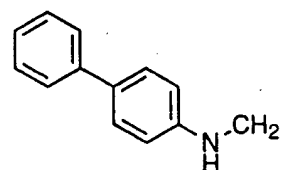
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699



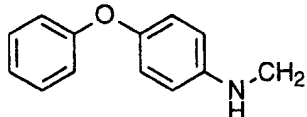
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700



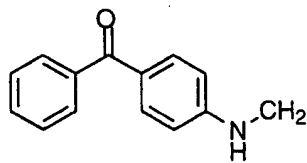
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701



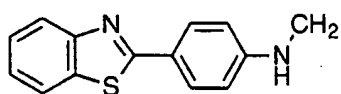
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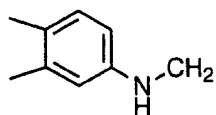
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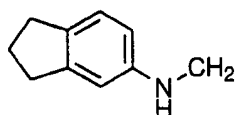
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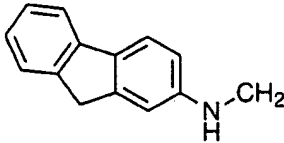
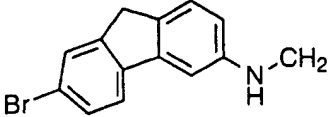
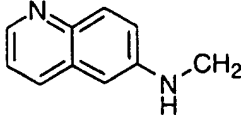
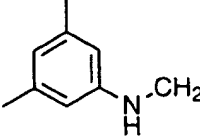
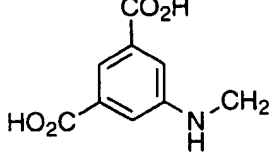
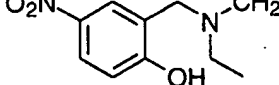
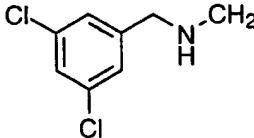
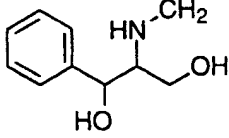
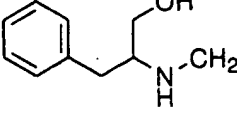
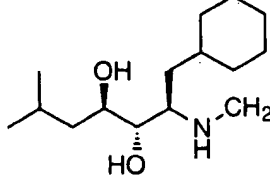
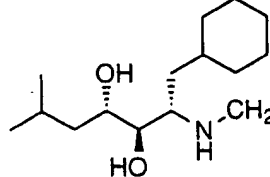


463

705

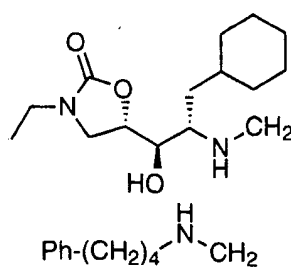


475

706		523
707		601
708		486
709		463
710		523
711		538
712		517
713		509
714		493
715		585
716		585

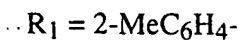
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601

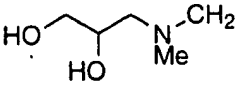
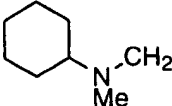
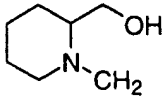
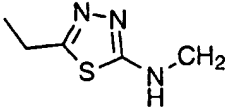
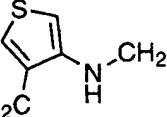
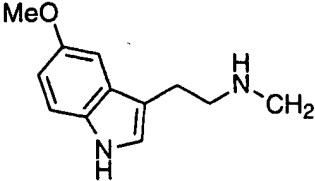
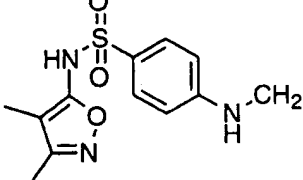
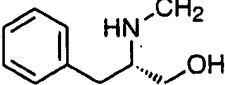


718

491



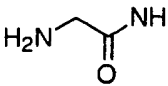
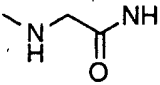
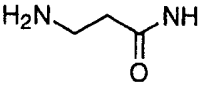
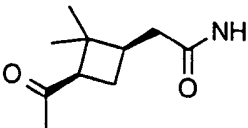
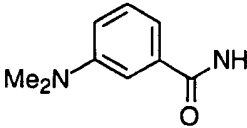
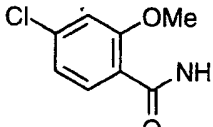
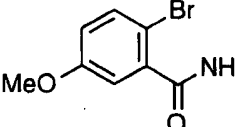
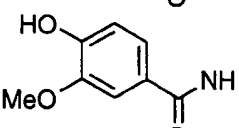
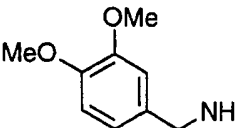
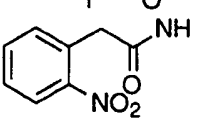
8265

<u>Example</u>	<u>R₃L₁</u>	<u>MS (M+H)⁺</u>
719		461
720		459
721		483
723		485
724		513
725		549
726		623
727		506

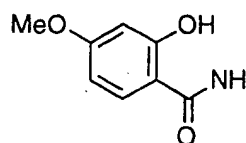
Examples 748-758 were prepared by the procedure described in Example 57

$R_1 = \text{Ph}$

8270

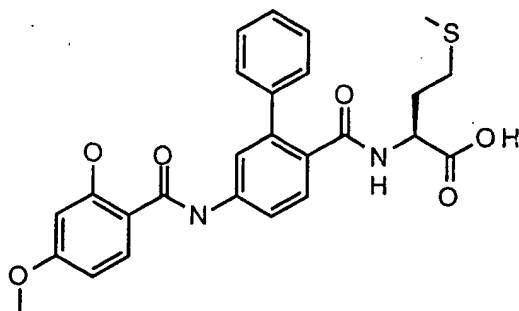
<u>Example</u>	<u>R_3L_1</u>	<u>MS (M+H)⁺</u>
748		402
749		416
750		416
751		511
752		492
753		513
754		558
755		489
756		635
757		508

758



489

8275

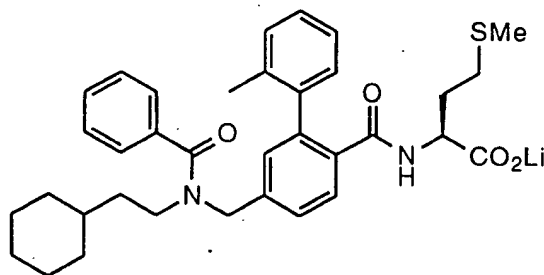
Example 759

(2S)-2-N-[4-(N-benzoyl-N-3-pyridylaminomethyl)-2-(2-methylphenyl)benzoyl]amino-4-methanesulfonylbutanoic acid.

8280

The desired compound was prepared according to the method of Example 157. ¹H (300 MHz., DMSO *d*₆): δ 12.8, (1H, s), 8.18, (1H, d J=8.Hz), 7.50 (2H, d, J=8Hz), 7.38 - 7.09 (14H, m), 4.83 (2H, s), 4.78 (2H, s), 4.21 (1H, s), 2.91 (3H, s), 2.76 (1H, m), 2.02, (1H, m), 2.00, (3H, s), 1.85 (2H, m). MS (DCI - NH₃) *m/z* 572 (MH⁺); Anal calcd for C₃₂H₃₃N₃O₅•1H₂O: C, 65.18. H, 5.98. N, 7.13 Found: C, 65.54; H, 5.73; N, 6.82.

8285



8290

Example 762

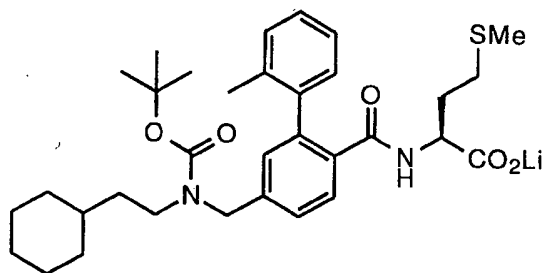
N-[4-N-Benzoyl-N-2-cyclohexylethylaminomethyl)-2-(2-methylphenyl)benzoyl]methionine lithium salt

The desired compound was prepared according to the method of Example 607. The resultant amine was reacted with benzoyl chloride - lithium carbonate under Schotten-Baumann conditions. MS (CI/NH₃) *m/z*: (M-H)⁻ 585; ¹H NMR (DMSO-*d*₆, 300 MHz) δ 7.53 (m, 1H), 7.45-7.32 (m, 6H), 7.25-7.08 (m, 4H), 6.94 (m, 1H), 4.73-4.68 (m, 2H),

8295

3.67-3.61 (m, 1H), 3.18-3.10 (m, 2H), 2.17-1.94 (m, 7H), 1.70-1.15 (m, 14H), 0.68-0.55 (m, 2H); Anal. Calcd for $C_{35}H_{41}LiN_2O_4S \cdot 1.80 H_2O$: C, 67.25; H, 7.19; N, 4.48. Found: C, 67.23; H, 6.78; N, 4.28.

8300



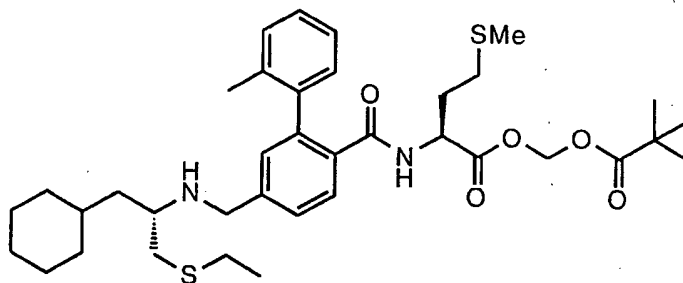
Example 763

N-[4-N-t-Butyloxycarbonyl-N-2-cyclohexylethylaminomethyl]-2-(2-methylphenyl)benzoyl]methionine lithium salt

8305

The desired compound was prepared according to the method of Example 607. The resultant amine was reacted with di-t-butyl dicarbonate under Schotten-Baumann conditions. MS (CI/NH₃) m/z: (M-H)⁻ 581; ¹H NMR (DMSO-d₆, 300 MHz) δ 7.51 (m, 1H), 7.31-6.93 (m, 6H), 4.41 (s, 2H), 3.69-3.61 (m, 1H), 3.25-3.13 (m, 2H), 2.14 (m, 1H), 2.02-1.91 (m, 2H), 1.91 (s, 3H), 1.66-1.51 (m, 8H), 1.45-1.05 (m, 16H), 0.88-0.75 (m, 2H); Anal. Calcd for $C_{23}H_{45}LiN_2O_5S \cdot 1.70 H_2O$: C, 64.00; H, 7.88; N, 4.52. Found: C, 63.99; H, 7.49; N, 4.33.

8310



8315

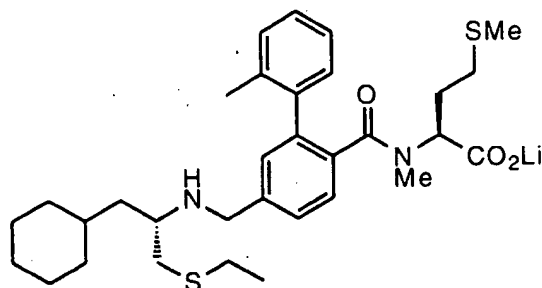
Example 764

Pivaloyloxymethyl N-[4-N-(3-Cyclohexyl-1-ethylthiopropyl)-N-methylaminomethyl]-2-(2-methylphenyl)benzoyl]-methionine hydrochloride salt

The desired compound was prepared by reaction of the compound resulting from Example 763 under conditions described in Example 500, followed by treatment with 4N HCl - dioxane. MS (CI/NH₃) m/z: (M+H)⁺ 671; ¹H NMR (DMSO-d₆, 300 MHz) δ 8.42 (d, J=7.5 Hz, 1H), 7.65 (d, J=8.1 Hz, 1H), 7.55 (d, J=7.5 Hz, 1H), 7.49-7.42 (m, 1H),

8320

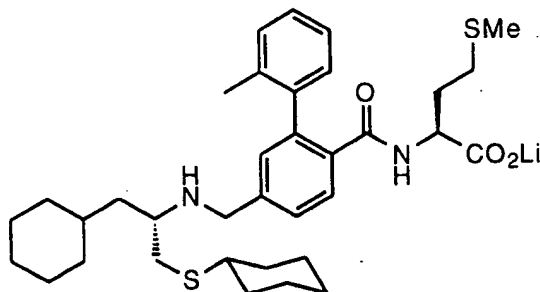
7.26-7.06 (m, 3H), 5.73 (d, J=5.8 Hz, 1H), 5.65 (d, J=5.8 Hz, 1H), 4.29 (brs, 2H), 3.25-3.17 (m, 1H), 3.04-2.97 (m, 1H), 2.86-2.77 (m, 1H), 2.24-2.02 (m, 6H), 1.94 (s, 3H), 1.83-1.40 (m, 12H), 1.25-1.07 (m, 6H), 1.13 (s, 9H), 0.93-0.77 (m, 2H); Anal. Calcd for C₃₇H₅₅ClN₂O₅S₂: C, 62.82; H, 7.84; N, 3.96. Found: C, 62.71; H, 8.03; N, 3.90.



Example 765

N-[4-N-(3-Cyclohexyl-1-ethylthiopropyl)-N-methylaminomethyl-2-(2-methylphenyl)benzoyl]-N-methylmethionine lithium salt

The desired compound was prepared according to the method of Example 158. MS (Cl/NH₃) m/z: (M-H)⁻ 569; ¹H NMR (DMSO-d₆, 300 MHz) δ 7.38 (d, J=7.8 Hz, 1H), 7.24-7.04 (m, 6H), 4.53-4.45 (m, 1H), 3.85-3.67 (m, 2H), 2.67-2.59 (m, 2H), 2.50-2.38 (m, 5H), 2.18-1.92 (m, 5H), 1.87 (s, 3H), 1.70-1.05 (m, 17H), 0.93-0.72 (m, 2H); Anal. Calcd for C₃₂H₄₅LiN₂O₃S₂•1.20 H₂O: C, 64.23; H, 7.98; N, 4.68. Found: C, 64.27; H, 7.97; N, 4.66.

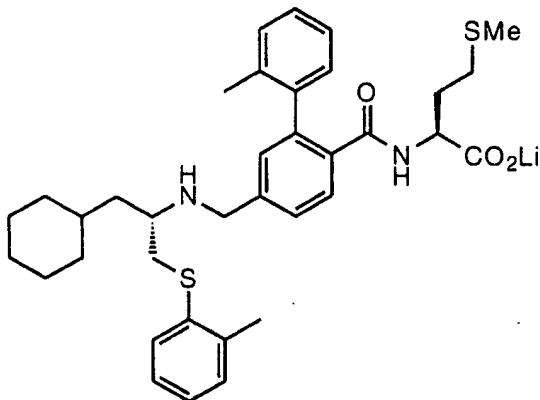


Example 766

N-[4-N-(3-Cyclohexyl-1-cyclohexylthiopropyl)-N-methylaminomethyl-2-(2-methylphenyl)benzoyl]methionine lithium salt

The desired compound was prepared according to the method of Example 158. MS (Cl/NH₃) m/z: (M-H)⁻ 609; ¹H NMR (DMSO-d₆, 300 MHz) δ 7.48 (d, J=7.7 Hz, 1H), 7.34 (m, 1H), 7.21-7.06 (m, 4H), 6.96-6.88 (m, 1H), 3.83-3.66 (m, 3H), 2.64-2.54 (m,

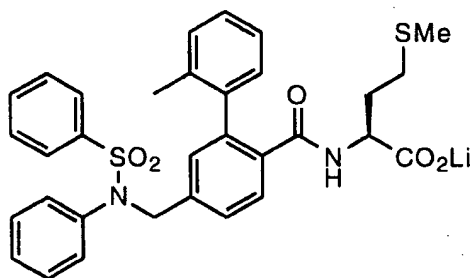
2H), 2.15-1.90 (m, 4H), 1.90 (s, 3H), 1.87-1.02 (m, 26H), 0.87-0.75 (m, 2H); Anal. Calcd for $C_{35}H_{49}LiN_2O_3S_2 \cdot 1.05 H_2O \cdot 1.60 TFA$: C, 56.08; H, 6.49; N, 3.42. Found: C, 56.05; H, 6.50; N, 3.49.



Example 767

8355 *N*-[4-*N*-(3-Cyclohexyl-1-(2-methylphenyl)thiopropyl)-2-(2-methylphenyl)benzoyl]methionine lithium salt

The desired compound was prepared according to the method of Example 158. MS (CI/NH₃) *m/z*: (M-H)⁻ 617; ¹H NMR (DMSO-d₆, 300 MHz) δ 7.45 (d, *J*=7.8 Hz, 1H), 7.32-6.85 (m, 10H), 3.82-3.64 (m, 3H), 3.06 (dd, *J*=12.5, 4.4 Hz, 1H), 2.88-2.78 (m, 1H), 2.74-2.62 (m, 1H), 2.23 (s, 3H), 2.16-2.08 (m, 2H), 1.97-1.90 (m, 2H), 1.92 (s, 3H), 1.85-0.98 (m, 14H), 0.90-0.63 (m, 2H); Anal. Calcd for $C_{36}H_{45}LiN_2O_3S_2 \cdot 1.0 H_2O$: C, 67.16; H, 7.51; N, 4.35. Found: C, 67.17; H, 7.30; N, 4.24.

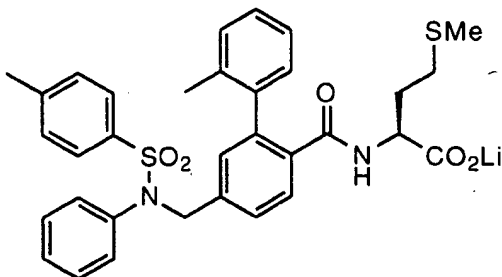


Example 769

8365 *N*-[4-*N*-(*N*-phenyl-*N*-benzenesulfonylaminomethyl)-2-(2-methylphenyl)benzoyl]methionine lithium salt

The desired compound was prepared according to the method of Example 157.
8370 ¹H(CD₃OD): δ 7.6-7.7 (2H, m); 7.5-7.6 (2H, m); 7.3-7.4 (1H, m); 7.3-7.1 (10H, m);

6.9-7.1 (2H, m); 4.9 (2H, s); 4.1-4.3 (1H, m); 2.1-1.5 (10H, m). ESI(-)/MS: 587(M-Li); 407.



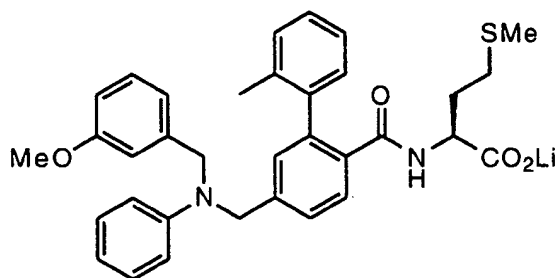
8375

Example 770

N-[4-N-(N-phenyl-N-toluenesulfonylaminomethyl)-2-(2-methylphenyl)benzoyl]methionine lithium salt

The desired compound was prepared according to the method of Example 157.

8380 $^1\text{H}(\text{CD}_3\text{OD})$: δ 7.6-7.7 (2H, m); 7.5-7.6 (2H, m); 7.3-7.4 (1H, m); 7.3-7.1 (10H, m); 6.9-7.1 (2H, m); 4.9 (2H, s); 4.1-4.3 (1H, m); 2.4 (3H, m); 1.5-2.1 (10H, m). ESI(-)/MS: 601(M-Li); 421



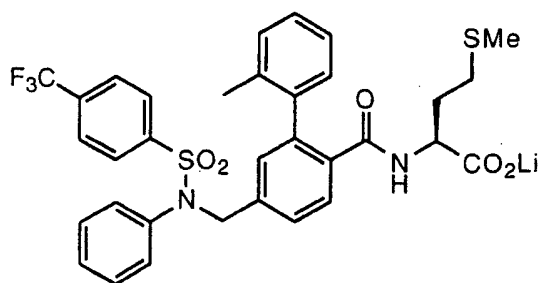
8385

Example 779

N-[4-N-(N-phenyl-N-(3-methoxybenzyl)aminomethyl)-2-(2-methylphenyl)benzoyl]methionine lithium salt

The desired compound was prepared according to the method of Example 157.

8390 $^1\text{H}(\text{MeOH-}d_4)$: δ 7.6-7.7 (1H, d); 7.3-7.4 (1H, d); 7.0-7.3 (8H, m); 6.6-6.85 (6H, m); 4.7 (2H, s); 4.65 (2H, s); 4.18-4.3 (1H, m); 3.65 (3H, s); 1.5-2.2 (10H, m). ESI(-)/MS: 567(M-Li); 447; 366; 281.



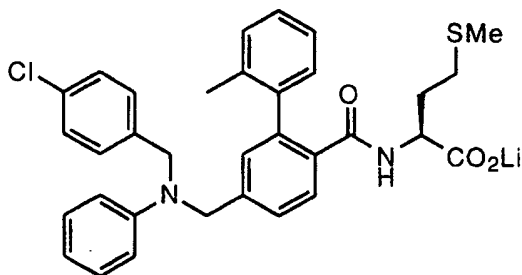
8395

Example 780

N-[4-N-(N-phenyl-N-(4-trifluoromethylbenzenesulfonyl)aminomethyl)-2-(2-methylphenyl)-benzoyl]methionine lithium salt

The desired compound was prepared according to the method of Example 157.

8400 ^1H (MeOH- d_4): δ 7.8-7.95 (4H, m); 7.5-7.6 (1H, d), 7.3-7.4 (1H, d); 7.1-7.3 (7H, m); 6.95-7.1 (3H, m); 4.9 (2H, s); 4.1-4.22 (1H, m); 1.7-2.1 (10H, m); 1.5-1.7 (1H, m). ESI(-)/MS: 655(M-Li); 475, 431.



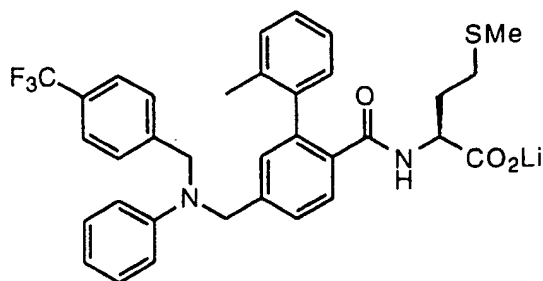
8405

Example 781

N-[4-N-(N-phenyl-N-(4-chlorobenzyl)aminomethyl)-2-(2-methylphenyl)benzoyl]methionine lithium salt

The desired compound was prepared according to the method of Example 157.

8410 ^1H (MeOH- d_4): δ 7.6-7.7 (1H, d); 7.3-7.4 (1H, d); 7.18-7.30 (6H, m); 7.0-7.2 (4H, m); 6.6-6.78 (4H, m); 4.71 (2H, s); 4.64 (2H, s); 4.2-4.3 (1H, m); 1.55-2.2 (10H, m). ESI(-)/MS: 571(M-Li); 367, 255.



8415

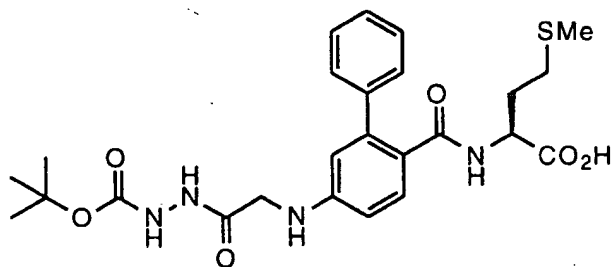
Example 782

N-[4-N-(N-phenyl-N-(4-trifluoromethylbenzyl)aminomethyl)-2-(2-methylphenyl)-benzoyl]methionine lithium salt

The desired compound was prepared according to the method of Example 157.

8420 ^1H (MeOH- d_4): δ 7.55-7.7 (3H, m); 7.3-7.5 (3H, m); 7.2-7.3 (3H, m); 7.0-7.18 (4H, m); 4.8 (4H, d); 4.18-4.3 (1H, m); 1.6-2.2 (10H, m).

ESI(-)/MS: 605(M-Li); 367; 283.



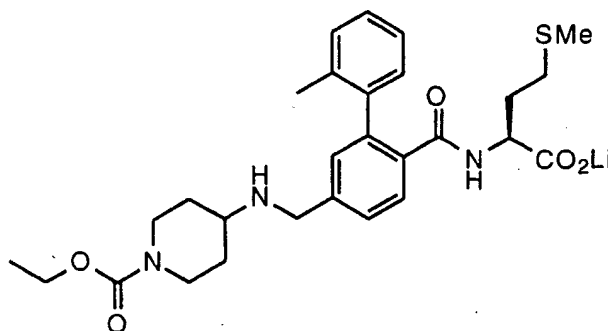
8425

Example 784

N-[4-N(t-Butylcarbazatocarbonylmethyl)amino-2-phenylbenzoyl]methionine

The desired compound was prepared according to the method of Example 57, except

8430 t-Butylcarbazatocarbonylmethyl bromide was used as the alkylating agent. ^1H nmr (300 MHz, DMSO- d_6): δ 9.79 (s, 1 H), 8.85 (s, 1 H), 8.12 (d, 1 H), 7.47-7.29 (m, 6 H), 6.65 (br d, 1 H), 6.56 (d, 1 H), 6.43 (t, 1 H), 4.30 (m, 1 H), 3.81 (d, 2 H), 2.32 (m, 2 H), 2.05 (br s, 6 H), 1.90 (m, 2 H), 1.47 (s, 9 H). MS (APCI +) m/e 517 (M+H) $^+$.



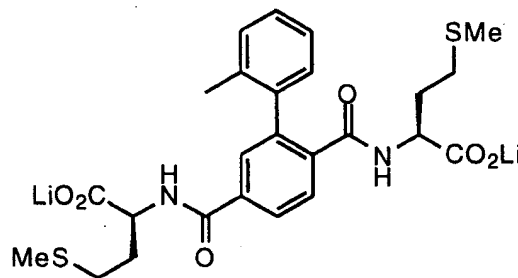
8435

Example 806

N-[4-(1-ethoxycarbonylpiperidin-4-ylaminomethyl)-2-(2-methylphenyl)benzoyl]methionine lithium salt

The desired compound was prepared according to the method of Example 158. ¹H nmr (300 MHz, DMSO-d₆): δ 7.48 (d, 1 H), 7.38 (dd, 1 H), 7.26-7.10 (m, 5 H), 6.90 (m, 1 H), 4.00 (q, 2 H), 3.88-3.73 (m, 4 H), 3.66 (m, 1 H), 2.85 (m, 2 H), 2.56 (m, 1 H), 2.18 (m, 2 H), 2.00 (m, 5 H), 1.92 (br s, 3 H), 1.80 (m, 1 H), 1.76 (m, 1 H), 1.68 (m, 1 H), 1.58 (m, 1 H), 1.16 (t, 3 H). MS (ESI⁻): m/e 526 (M-H)⁻.

8440



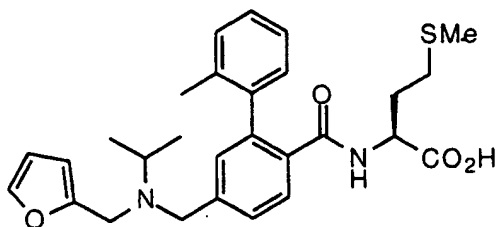
8445

Example 830

N-[4-(N-[3-methylthio-1-carboxyprop-2-yl]aminocarbonyl)-2-phenylbenzoyl]methionine

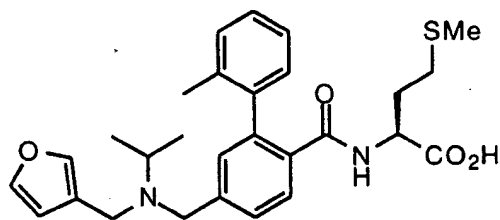
The desired compound was prepared according to the method of Example 451. ¹H NMR (d₆-DMSO): δ 1.64-1.91 (comp, 2 H), 1.93 (s, 3 H), 1.98-2.22 (comp, 10 H), 2.46-2.62 (comp, 2 H), 4.18-4.28 (m, 1 H), 4.49-4.58 (m, 1 H), 7.14-7.26 (comp, 4 H), 7.58 (d, *J* = 7.8 Hz, 1 H), 7.74-7.79 (br s, 1 H), 7.96 (dd, *J* = 1.7, 7.8 Hz, 1 H), 8.24-8.32 (br, 1 H), 8.74 (d, *J* = 7.4 Hz, 1 H), 12.50-12.93 (br, 2 H). LRMS (ESI⁻): 517 (M-1)⁻.

8450

**Example 831**

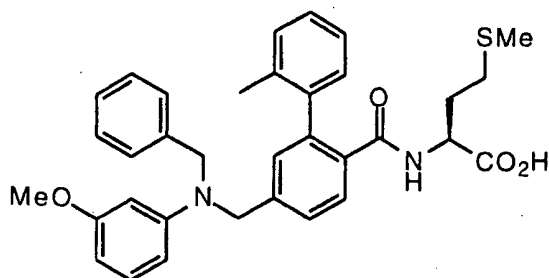
N-[4-*N*-(furan-2-ylmethyl)-*N*-isopropylaminomethyl]-2-(2-methylphenyl)benzoyl]methionine
lithium salt

The desired compound was prepared according to the method of Example 158. ¹H NMR (d₆-DMSO): δ 1.00 (d, *J*= 6.6 Hz, 6 H), 1.50-1.63 (m, 1 H), 1.63-1.76 (m, 1 H), 1.77-2.18 (comp, 8 H), 2.89 (sept, *J*= 6.6 Hz, 1 H), 3.56 (s, 2 H), 3.63 (s, 2 H), 3.66-3.80 (br, 1 H), 6.23 (d, *J*= 2.9 Hz, 1 H), 6.35 (dd, *J*= 1.8, 3.3 Hz, 1 H), 6.93 (d, *J*= 6.2 Hz, 1 H), 7.10-7.26 (br comp, 4 H), 7.37 (d, *J*= 8.1 Hz, 1 H), 7.48 (d, *J*= 7.7 Hz, 1 H), 7.53 (dd, *J*= 0.7, 1.8 Hz, 1 H). LRMS (ESI⁻): 493 (M-1)⁻.

**Example 832**

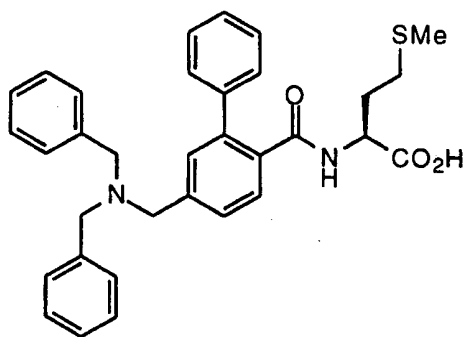
N-[4-*N*-(furan-3-ylmethyl)-*N*-isopropylaminomethyl]-2-(2-methylphenyl)benzoyl]methionine
lithium salt

The desired compound was prepared according to the method of Example 158. ¹H NMR (d₆-DMSO): δ 1.00 (d, *J*= 6.6 Hz, 6 H), 1.49-1.76 (comp, 2 H), 1.76-2.19 (comp, 8 H), 2.88 (sept, *J*= 6.6 Hz, 1 H), 3.37 (s, 2 H), 3.57 (s, 2 H), 3.68-3.78 (br, 21 H), 6.36 (s, 1 H), 6.93 (d, *J*= 6.2 Hz, 1 H), 7.08-7.26 (comp, 4 H), 7.39 (d, *J*= 8.1 Hz, 1 H), 7.48 (d, *J*= 7.6 Hz, 1 H), 7.52-7.57 (comp, 2 H). LRMS (ESI⁻): 493 (M-1)⁻.

**Example 833**

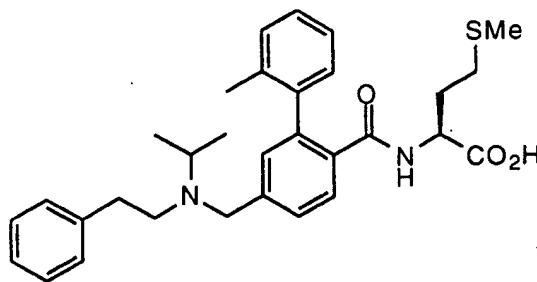
8480 *N*-[4-*N*-benzyl-*N*-3-methoxyphenylaminomethyl-2-(2-methylphenyl)benzoyl]methionine
 lithium salt

The desired compound was prepared according to the method of Example 157. ¹H NMR (d₆-DMSO): δ 1.48-2.10 (comp, 10 H), 3.60 (s, 3 H), 3.64-3.74 (br, 1 H), 4.69 (s, 2 H), 4.75 (s, 2 H), 6.15-6.18 (br comp, 2 H), 6.20 (d, *J* = 1.9 Hz, 1 H), 6.29 (dd, *J* = 2.3, 9.2 Hz, 1 H), 6.90-7.03 (comp, 3 H), 7.08-7.34 (comp, 9 H), 7.50 (d, *J* = 7.7 Hz, 1 H). LRMS (ESI⁻): 467 (M-1)⁻.

**Example 834**

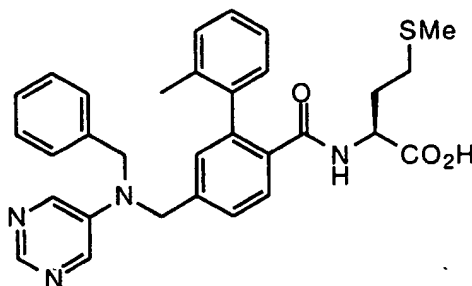
8490 *N*-[4-*N,N*-dibenzylaminomethyl-2-phenylbenzoyl]methionine lithium salt

The desired compound was prepared according to the method of Example 158. ¹H NMR (d₆-DMSO): δ 1.74-1.95 (comp, 2 H), 1.99 (s, 3 H), 2.15-2.34 (comp, 2 H), 4.17-4.37 (comp, 6 H), 7.21-7.55 (comp, 14 H), 7.60-7.75 (comp, 4 H), 8.57 (d, *J* = 7.8 Hz, 1 H). LRMS (CI⁺): 539 (M+1)⁺.

Example 835

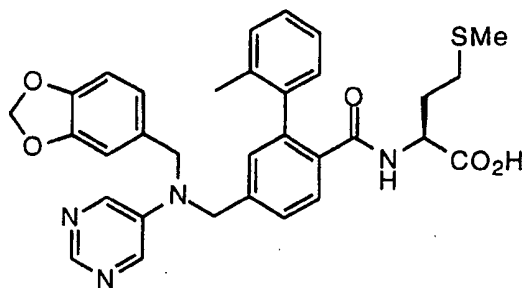
8500 N-[4-N-(2-phenylethyl)-N-isopropylaminomethyl]-2-(2-methylphenyl)benzoyl]methionine
lithium salt

The desired compound was prepared according to the method of Example 158. ¹H NMR (d₆-DMSO): δ 0.94 (d, *J* = 6.3 Hz, 6 H), 1.50-1.77 (comp, 2 H), 1.77-2.20 (comp, 8 H), 2.56-2.66 (comp, 4 H), 2.92 (sept, *J* = 6.3 Hz, 1 H), 3.66 (s, 2 H), 3.70-3.81 (br, 1 H), 6.94 (d, *J* = 5.9 Hz, 1 H), 7.07-7.26 (comp, 9 H), 7.32 (d, *J* = 7.7 Hz, 1 H), 7.46 (dd, *J* = 1.8, 7.7 Hz, 1 H). LRMS (ESI⁻): 517 (M-1)⁻.

Example 836

8510 N-[4-N-benzyl-N-pyrimidin-5-ylaminomethyl]-2-(2-methylphenyl)benzoyl]methionine
lithium salt

The desired compound was prepared according to the method of Example 157. ¹H NMR (d₆-DMSO): δ 1.48-1.74 (br comp, 2 H), 1.86-2.08 (br comp, 8 H), 3.62-3.74 (br, 1 H), 4.83 (s, 2 H), 4.89 (s, 2 H), 6.92-7.03 (br, 1 H), 7.04-7.38 (comp, 11 H), 7.52 (d, *J* = 8.1 Hz, 1 H), 8.22 (s, 2 H), 8.42 (s, 1 H). LRMS (ESI⁻): 539 (M-1)⁻.



8520

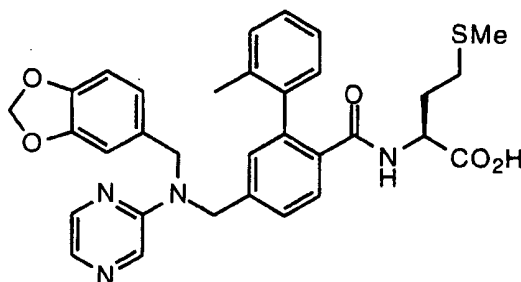
Example 837

N-[4-*N*-(1,3-benzodiox-5-yl)-*N*-pyrimidin-5-ylaminomethyl-2-(2-methylphenyl)benzoyl]methionine lithium salt

8525

The desired compound was prepared according to the method of Example 157. ¹H NMR (d₆-DMSO): δ 1.46-1.76 (br comp, 2 H), 1.84-2.05 (br comp, 8 H), 3.56-3.67 (br, 1 H), 4.71 (s, 2 H), 4.86 (s, 2 H), 6.77 (dd, *J* = 1.6, 7.8 Hz, 1 H), 6.83-6.88 (comp, 2 H), 6.90-6.98 (br comp, 2 H), 7.0 (s, 1 H), 7.07-7.24 (br comp, 3 H), 7.33 (dd, *J* = 1.9, 8.1 Hz, 1 H), 7.51 (d, *J* = 7.7 Hz, 1 H), 8.23 (s, 2 H), 8.42 (s, 1 H). LRMS (ESI⁻): 583 (M-1)⁻.

8530

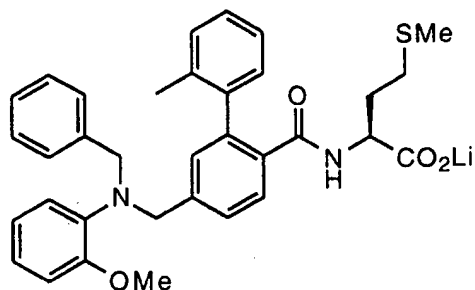
Example 838

N-[4-*N*-(1,3-benzodiox-5-yl)-*N*-pyridizin-2-ylaminomethyl-2-(2-methylphenyl)benzoyl]methionine lithium salt

8535

The desired compound was prepared according to the method of Example 157. ¹H NMR (d₆-DMSO): δ 1.49-1.72 (comp, 2 H), 1.88-2.06 (comp, 8 H), 3.60-3.71 (br, 1 H), 4.75-4.80 (br, 2 H), 4.90 (s, 2 H), 5.96 (s, 2 H), 6.75 (dd, *J* = 1.7, 7.8 Hz, 1 H), 6.80-6.83 (comp, 2 H), 6.90-6.96 (comp, 3 H), 7.05-7.22 (br, 3 H), 7.29 (dd, *J* = 1.7, 8.2 Hz, 1 H), 7.49 (d, *J* = 7.8 Hz, 1 H), 7.80 (d, *J* = 2.4 Hz, 1 H), 8.03-8.09 (comp, 2 H).

8540

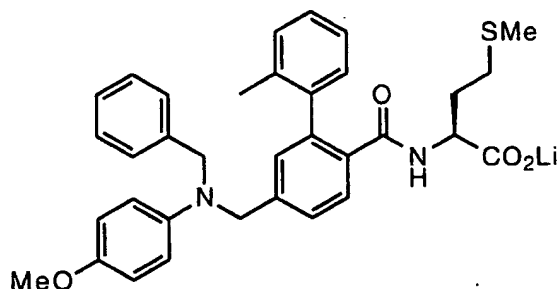
**Example 839**

N-[4-(*N*-benzyl-*N*-(2-methoxyphenyl)aminomethyl)-2-(2-methylphenyl)benzoyl]methionine
lithium salt

8545

The desired compound was prepared according to the method of Example 157. ¹H NMR (d₆-DMSO): δ 1.47-1.75 (comp, 2 H), 1.76-2.05 (comp, 8 H), 3.66-3.77 (br, 1 H), 3.83 (s, 3 H), 4.22 (s, 2 H), 4.26 (s, 2 H), 6.68-6.74 (m, 1 H), 6.81-6.98 (comp, 4 H), 7.02-7.08 (br, 1 H), 7.10-7.37 (comp, 9 H), 7.44 (d, *J* = 7.8 Hz, 1 H).

8550

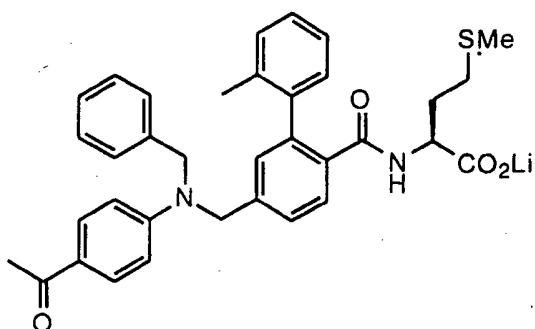
**Example 840**

N-[4-(*N*-benzyl-*N*-(4-methoxyphenyl)aminomethyl)-2-(2-methylphenyl)benzoyl]methionine
lithium salt

8555

The desired compound was prepared according to the method of Example 157. ¹H NMR (d₆-DMSO): δ 1.49-1.62 (m, 1 H), 1.62-1.75 (m, 1 H), 1.78-2.08 (comp, 8 H), 3.61 (s, 3 H), 3.64-3.76 (br, 1 H), 4.58 (s, 2 H), 4.64 (s, 2 H), 6.62-6.74 (comp, 4 H), 6.89-6.96 (m, 1 H), 7.01 (s, 1 H), 7.08-7.33 (comp, 9 H), 7.47 (d, *J* = 7.8 Hz, 1 H).

8560

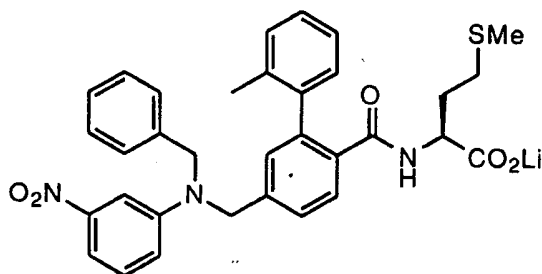
**Example 841**

N-[4-(*N*-benzyl-*N*-(4-acetylphenyl)aminomethyl)-2-(2-methylphenyl)benzoyl]methionine
lithium salt

8565

The desired compound was prepared according to the method of Example 157. ¹H NMR (d₆-DMSO): δ 1.48-1.63 (m, 1 H), 1.63-1.75 (m, 1 H), 1.78-2.10 (comp, 8 H), 2.38 (s, 3 H), 3.66-3.76 (br, 1 H), 4.82 (s, 2 H), 4.88 (s, 2 H), 6.74 (d, *J*= 8.8 Hz, 2 H), 6.95 (d, *J*= 6.1 Hz, 1 H), 7.02 (s, 1 H), 7.08-7.36 (comp, 9 H), 7.52 (d, *J*= 8.1 Hz, 1 H), 7.72 (d, *J*= 8.8 Hz, 2 H).

8570

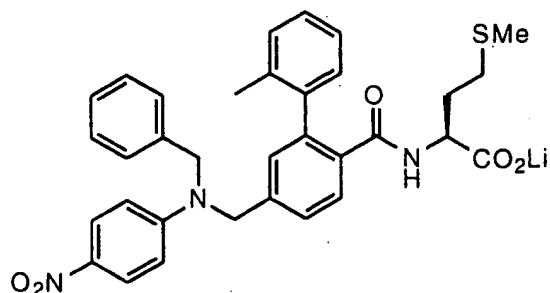
**Example 842**

N-[4-(*N*-benzyl-*N*-(3-nitrophenyl)aminomethyl)-2-(2-methylphenyl)benzoyl]methionine
lithium salt

8575

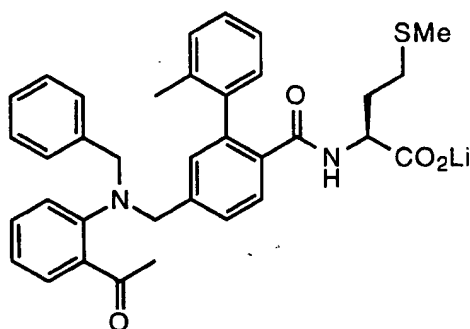
The desired compound was prepared according to the method of Example 157. ¹H NMR (d₆-DMSO): δ 1.49-1.76 (comp, 2 H), 1.77-2.08 (comp, 8 H), 3.67-3.76 (br, 1 H), 4.85 (s, 2 H), 4.90 (s, 2 H), 6.92-7.01 (br, 1 H), 7.05-7.43 (comp, 14 H), 7.53 (d, *J*= 7.8 Hz, 1 H).

8580

Example 843

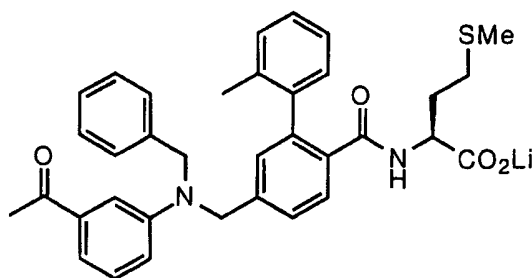
8585 N-[4-(N-benzyl-N-(4-nitrophenyl)aminomethyl)-2-(2-methylphenyl)benzoyl]methionine
lithium salt

The desired compound was prepared according to the method of Example 157. ¹H NMR (d₆-DMSO): δ 1.48-1.62 (m, 1 H), 1.62-1.74 (m, 1 H), 1.76-2.10 (comp, 8 H), 3.64-3.73 (br, 1 H), 4.90 (s, 2 H), 4.95 (s, 2 H), 6.82 (d, J= 9.5 Hz, 2 H), 6.94 (d, J= 6.1 Hz, 1 H), 7.02 (s, 1 H), 7.08-7.38 (comp, 9 H), 7.53 (d, J= 7.8 Hz, 1 H), 8.00 (d, J= 9.5 Hz, 2 H).

Example 844

8595 N-[4-N-(N-benzyl-N-(2-acetylphenyl)aminomethyl)-2-(2-methylphenyl)benzoyl]methionine
lithium salt

8600 The desired compound was prepared according to the method of Example 157. ¹H NMR (d₆-DMSO): δ 1.45-1.70 (br comp, 2 H), 1.86-2.04 (comp, 8 H), 2.60 (s, 3 H), 3.56-3.66 (br, 1 H), 4.21 (app s, 4 H), 6.82-6.94 (br comp, 2 H), 6.99 (t, J= 7.4 Hz, 1 H), 7.08 (d, J= 7.7 Hz, 1 H), 7.16-7.34 (comp, 10 H), 7.39 (dd, J= 1.9, 7.7 Hz, 1 H), 7.45 (d, J= 8.0 Hz, 1 H).



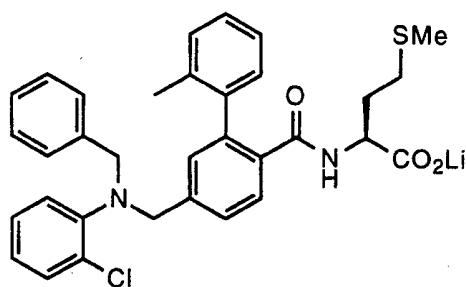
8605

Example 845

N-[4-N-(N-benzyl-N-(3-acetylphenyl)aminomethyl)-2-(2-methylphenyl)benzoyl]methionine
lithium salt

The desired compound was prepared according to the method of Example 157. ¹H NMR (d₆-DMSO): δ 1.48-1.74 (br comp, 2 H), 1.85-2.08 (comp, 8 H), 2.43 (s, 3 H), 3.62-3.74 (br, 1 H), 4.78 (s, 2 H), 4.84 (s, 2 H), 6.90-7.04 (comp, 2 H), 7.07-7.36 (comp, 13 H), 7.51 (d, J = 7.8 Hz, 1 H)

8610



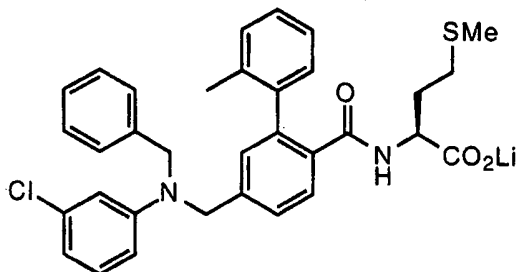
8615

Example 846

N-[4-N-(N-benzyl-N-(2-chlorophenyl)aminomethyl)-2-(2-methylphenyl)benzoyl]methionine
lithium salt

The desired compound was prepared according to the method of Example 157. ¹H NMR (d₆-DMSO): δ 1.46-1.64 (br comp, 2 H), 1.76-2.03 (comp, 8 H), 3.15-3.19 (br, 1 H), 4.23 (s, 2 H), 4.26 (s, 2 H), 6.84-7.47 (comp, 16 H).

8620

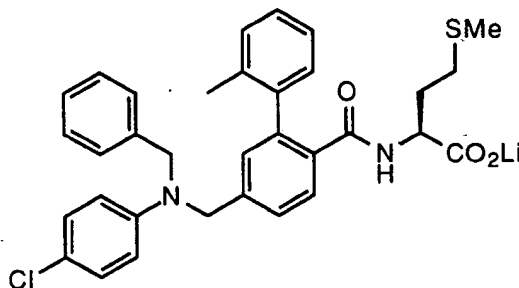


8625

Example 847

N-[4-*N*-(*N*-benzyl-*N*-(3-chlorophenyl)aminomethyl)-2-(2-methylphenyl)benzoyl]methionine
lithium salt

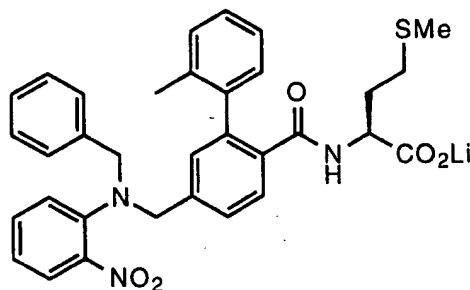
The desired compound was prepared according to the method of Example 157. ¹H NMR (d₆-DMSO): δ 1.48-1.75 (br comp, 2 H), 1.88-2.10 (comp, 8 H), 3.64-3.75 (br, 1 H), 4.74 (s, 2 H), 4.79 (s, 2 H), 6.57-6.66 (comp, 3 H), 6.90-7.36 (comp, 12 H), 7.52 (d, *J* = 7.7 Hz, 1 H).



Example 848

N-[4-*N*-(*N*-benzyl-*N*-(4-chlorophenyl)aminomethyl)-2-(2-methylphenyl)benzoyl]methionine
lithium salt

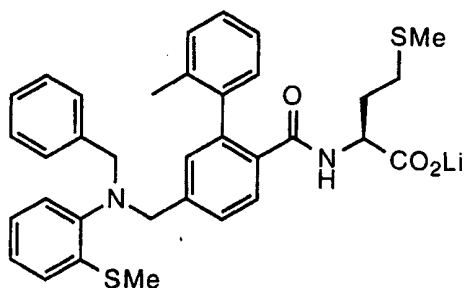
The desired compound was prepared according to the method of Example 157. ¹H NMR (d₆-DMSO): δ 1.47-1.76 (br comp, 2 H), 1.89-2.10 (comp, 8 H), 3.65-3.77 (br, 1 H), 4.71 (s, 2 H), 4.77 (s, 2 H), 6.62-6.89 (comp, 2 H), 6.90-7.34 (comp, 13 H), 7.51 (d, *J* = 7.8 Hz, 1 H).



Example 849

N-[4-*N*-(*N*-benzyl-*N*-(2-nitrophenyl)aminomethyl)-2-(2-methylphenyl)benzoyl]methionine
lithium salt

The desired compound was prepared according to the method of Example 157. ¹H NMR (d₆-DMSO): δ 1.46-1.71 (br comp, 2 H), 1.86-2.20 (br comp, 8 H), 3.58-3.70 (br, 1 H), 4.25 (s, 2 H), 4.27 (s, 2 H), 6.85-6.95 (br, 1 H), 6.98-7.36 (comp, 12 H), 7.45 (d, *J* = 7.8 Hz, 2 H), 7.75 (dd, *J* = 1.7, 8.2 Hz, 1 H).

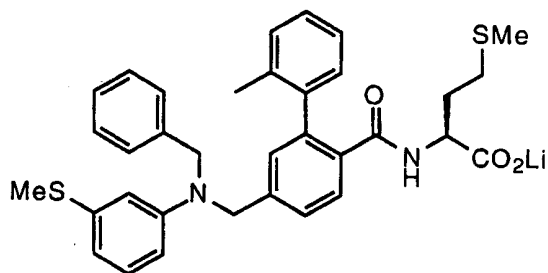


8655

Example 850*N*-[4-(*N*-benzyl-*N*-(2-methylthiophenyl)aminomethyl)-2-(2-methylphenyl)benzoyl]methionine lithium salt

The desired compound was prepared according to the method of Example 157. ¹H NMR (d₆-DMSO): δ 1.48-1.72 (br comp, 2 H), 1.86-2.03 (br comp, 8 H), 2.40 (s, 3 H), 3.58-3.68 (br, 1 H), 4.09 (s, 2 H), 4.13 (s, 2 H), 6.83-6.91 (br, 1 H), 6.95-7.31 (comp, 11 H), 7.33-7.44 (comp, 4 H).

8660

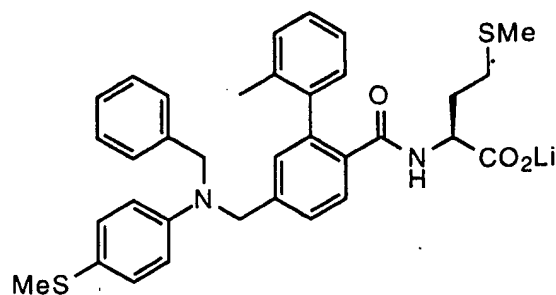


8665

Example 851*N*-[4-(*N*-benzyl-*N*-(3-methylthiophenyl)aminomethyl)-2-(2-methylphenyl)benzoyl]methionine lithium salt

The desired compound was prepared according to the method of Example 157. ¹H NMR (d₆-DMSO): ¹H NMR (d₆-DMSO): δ 1.48-1.72 (br comp, 2 H), 1.89-2.09 (br comp, 8 H), 2.27 (s, 3 H), 3.62-3.71 (br, 1 H), 4.71 (s, 2 H), 4.77 (s, 2 H), 6.45-6.49 (comp, 3 H), 6.91-7.35 (comp, 12 H), 7.50 (d, J = 8.1 Hz, 1 H).

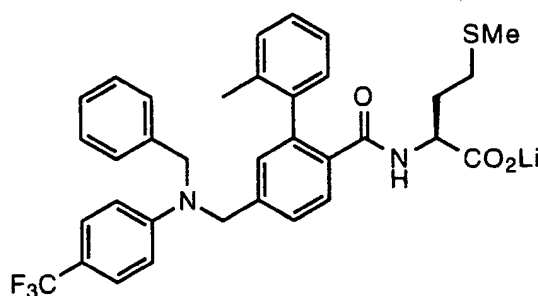
8670



Example 852

N-[4-(N-benzyl-N-(4-methylthiophenyl)aminomethyl)-2-(2-methylphenyl)benzoyl]methionine lithium salt

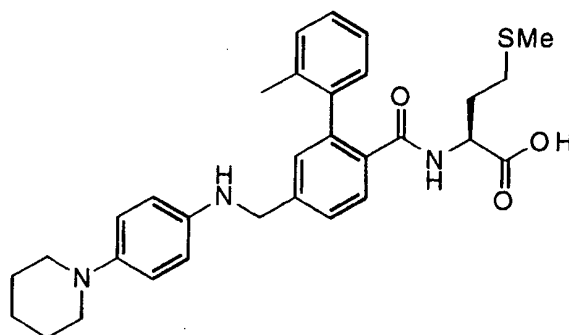
The desired compound was prepared according to the method of Example 157. ¹H NMR (d₆-DMSO): δ 1.45-1.74 (br comp, 2 H), 1.88-2.08 (br comp, 8 H), 2.33 (s, 3 H), 3.58-3.67 (br, 1 H), 4.70 (s, 2 H), 4.76 (s, 2 H), 6.64 (d, J = 8.8 Hz, 2 H), 6.88-6.94 (br, 1 H), 7.00 (s, 1 H), 7.10 (d, J = 8.8 Hz, 2 H), 7.16-7.34 (comp, 9 H), 7.50 (d, J = 7.8 Hz, 1 H).



Example 853

N-[4-(N-benzyl-N-(4-trifluoromethylphenyl)aminomethyl)-2-(2-methylphenyl)benzoyl]methionine lithium salt

The desired compound was prepared according to the method of Example 157. ¹H NMR (d₆-DMSO): δ 1.48-1.75 (br comp, 2 H), 1.90-2.06 (br comp, 8 H), 3.64-3.74 (br, 1 H), 4.81 (s, 2 H), 4.86 (s, 2 H), 6.79 (d, J = 8.8 Hz, 2 H), 6.90-7.35 (comp, 11 H), 7.40 (d, J = 8.8 Hz, 2 H), 7.52 (d, J = 7.8 Hz, 1 H).

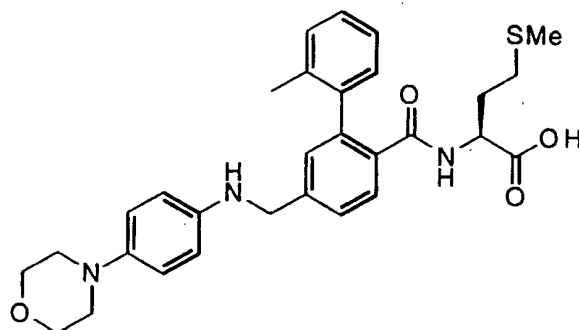


8695

Example 862**N-[4-N-(4-piperidin-1-ylphenyl)aminomethyl-2-(2-methylphenyl)benzoyl]methionine**

The desired compound was prepared according to the method of Example 158. MS m/e 530 (M-H)⁻. ¹H NMR (CDCl₃, 300 MHz) δ 1.55 (m, 3H), 1.78 (m, 4H), 1.85 (m, 1H), 2.0 (m, 8H), 3.03 (m, 4H), 4.3 (m, 3H), 6.13 (m, 1H), 6.54 (m, 2H), 6.98 (m, 2H), 7.10-7.52 (m, 6H), 7.74 (m, 1H).

8700

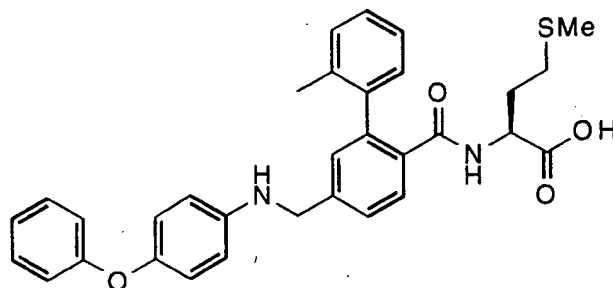


8705

Example 863**N-[4-N-(4-morpholin-1-ylphenyl)aminomethyl-2-(2-methylphenyl)benzoyl]methionine**

The desired compound was prepared according to the method of Example 158. MS m/e 534 (M+H)⁺. ¹H NMR (CDCl₃, 300 MHz) δ 1.48 (m, 1H), 1.83 (m, 1H), 2.0 (m, 8H), 3.00 (m, 4H), 3.85 (m, 4H), 4.35 (m, 3H), 6.03 (m, 1H), 6.58 (m, 2H), 6.80 (m, 2H), 7.22 (m, 6H), 7.85 (m, 1H).

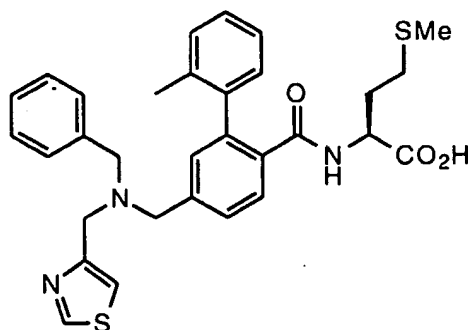
8710

Example 864

8715 N-[4-N-(4-phenoxyphenyl)aminomethyl-2-(2-methylphenyl)benzoyl]methionine

The desired compound was prepared according to the method of Example 158. MS m/e 539 (M-H)⁻. ¹H NMR (CDCl₃, 300 MHz) δ 1.42 (m, 1H), 1.75 (m, 1H), 2.0 (m, 8H), 4.21 (m, 1H), 4.31 (s, 2H), 6.15 (m, 1H), 6.54 (m, 2H), 6.86 (m, 4H), 6.99 (m, 2H), 7.2 (m, 7H), 7.76 (m, 1H).

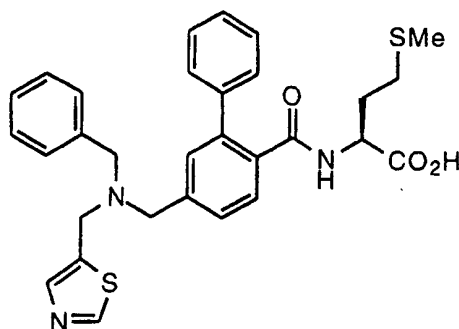
8720

Example 875

N-[4-N-(benzyl-N-thiazol-2-ylmethyl)aminomethyl-2-(2-methylphenyl)benzoyl]methionine

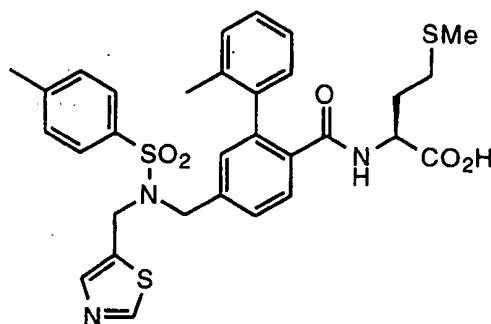
8725 The desired compound was prepared according to the method of Example 158. ¹H (300 MHz, DMSO d₆): δ 9.08, d, 1H; 8.13, d, 1H; 7.58, d, 1H; 7.49, s, 2H; 7.40, d, 2H; 7.31, t, 2H; 7.22, m, 4H; 7.11, m, 2H; 4.21, m, 1H; 3.77, s, 2H; 3.67, s, 2H; 3.62, s, 2H; 1.98 - 2.23, m, 5H; 1.97, s, 3H; 1.63 - 1.90, m, 2H. MS (ESI(-)): 558 (M-H). Calc'd for C₃₁H₃₃N₃O₃S₂ + 0.49 H₂O: C 65.49, H 6.02, N 7.39: Found: C 65.49, H 5.86, N 7.27.

8730

Example 876

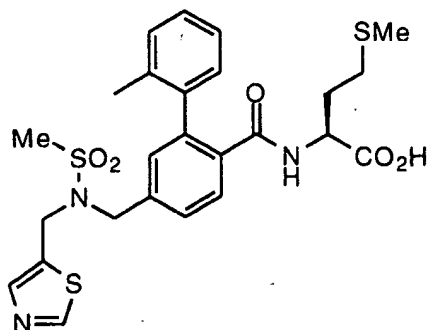
8735 N-[4-N-(benzyl-N-thiazol-5-ylmethyl)aminomethyl-2-phenylbenzoyl]methionine

The desired compound was prepared according to the method of Example 158. ¹H (300 MHz, DMSO d₆): δ 9.04, s, 1H; 8.46, d, 1H; 7.82, s, 1H; 7.3, m, 13H; 4.27, ddd, 1H; 3.83, s, 2H; 3.64, s, 2H; 3.60, s, 2H; 2.21, m, 2H; 1.99, s, 3H; 1.84, m, 2H. MS (ESI(-)): 544 (M-H). Calc'd for C₃₀H₃₁N₃O₃S₂: C 66.03, H 5.72, N 7.70: Found: C 65.65, H 5.81, N 7.50.

Example 877

8745 N-[4-N-(toluenesulfonyl-N-thiazol-2-ylmethyl)aminomethyl-2-(2-methylphenyl)benzoyl]methionine

The desired compound was prepared according to the method of Example 157. ¹H (300 MHz, DMSO d₆): δ 12.62, bs, 1H; 8.94, s, 1H; 8.08, bs, 1H; 7.79, d, 2H; 7.59, s, 1H; 7.41, m, 3H; 7.20, m, 4H; 7.03, bs, 1H; 6.90, bs, 1H; 4.59, s, 2H; 4.38, s, 2H; 4.21, m, 1H; 2.51, s, 3H; 2.40, s, 3H; 2.18, m, 2H; 1.98, s, 3H; 1.78, m, 2H. MS (ESI(-)): 622 (M-H). Calc'd for C₃₁H₃₃N₃O₅S₃: C 59.69, H 5.33, N 6.74: Found: C 59.41, H 5.19, N 6.57.

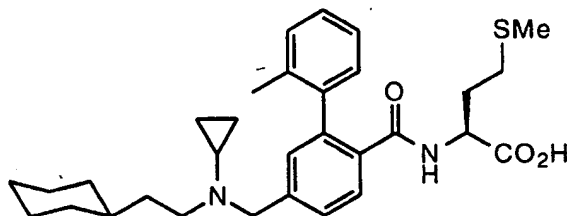


8755

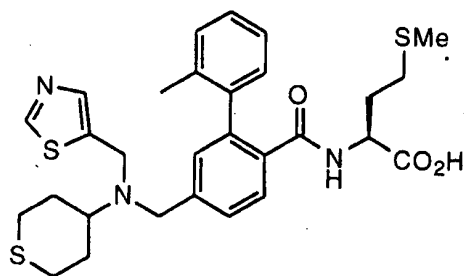
Example 878N-[4-N-(methanesulfonyl)-N-thiazol-2-ylmethyl]aminomethyl-2-(2-methylphenyl)-benzoyl]methionine

8760 The desired compound was prepared according to the method of Example 157. ¹H (300 MHz, DMSO d₆): δ 9.00, s, 1H; 8.11, bs, 1H; 7.52, s, 1H; 7.46, d, 1H; 7.39, dd, 1H; 7.00 - 7.22, m, 5H; 4.63, s, 2H; 4.42, s, 2H; 4.21, m, 1H; 3.02, s, 3H; 1.98 - 2.23, m, 5H; 1.97, s, 3H; 1.64 - 1.91, m, 2H. MS (ESI(-)): 546 (M-H); (ESI(+)): 548. Calc'd for C₂₅H₂₉N₃O₅S₃: C 54.82, H 5.34, N 7.67: Found: C 54.60, H 5.32, N .49.

8765

Example 880N-[4-(N-2-Cyclohexylethyl)-N-cyclopropylaminomethyl]-2-(2-methylphenyl)benzoyl]methionine

8770 The desired compound was prepared according to the method of Example 158. ¹H (300 MHz, DMSO d₆): δ 8.06, d, 1H; 7.47, d, 1H; 7.31, dd, 1H; 7.20, m, 2H; 7.02 - 7.17, m, 3H; 4.21, m, 1H; 3.71, s, 2H; 2.50, m, 2H; 1.98 - 2.23, m, 6H; 1.97, s, 3H; 1.68 - 1.90, m, 3H; 1.50 - 1.66, m, 4H; 1.37, m, 2H; 1.03 - 1.14, m, 4H; 0.81, m, 2H; 0.44, m, 2H; 0.30, m, 2H. MS (ESI(-)): 521 (M-H); ESI((+)): 523 (MH⁺). Calc'd for 8775 C₃₁H₄₂N₃O₃S: C 71.23, H 8.10, N 5.36: Found: C 70.25, H 8.05, N 5.31.

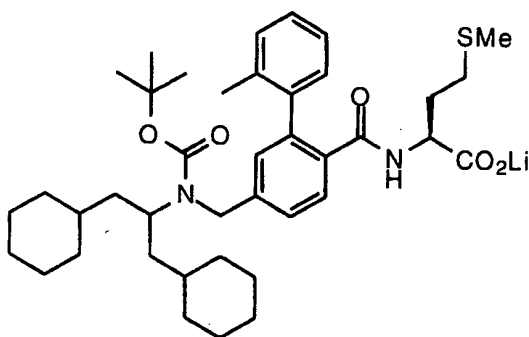
**Example 881**

8780

N-[4-(N-tetrahydrothiopyran-4-yl)-N-thiazol-5-ylaminomethyl]-2-(2-methylphenyl)benzoyl]methionine

The desired compound was prepared according to the method of Example 158. ¹H (300 MHz, DMSO d₆): δ 8.97, s, 1H; 8.08, d, 1H; 7.78, s, 1H; 7.44, dd, 2H; 7.00 - 7.25, m, 5H; 4.20, ddd, 1H; 3.89, s, 2H; 3.71, s, 2H; 2.38 - 2.70, m, 5H; 1.98 - 2.23, m, 7H; 1.97, s, 3H; 1.59 - 1.91, m, 4H. MS (ESI(-)): 5688 (M-H); ESI(+): 570. Calc'd for C₂₉H₃₅N₃O₃S₃ + 0.45 H₂O: C 60.27, H 6.26, N 7.27; Found: C 60.27, H 6.32, N 7.17.

8785

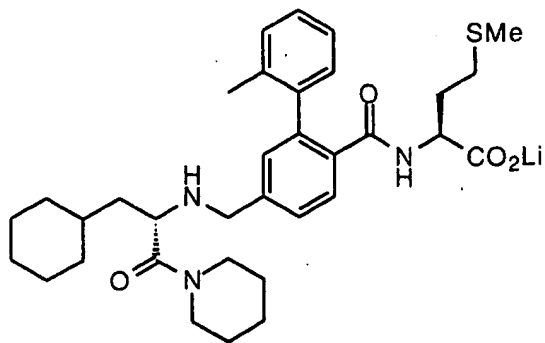


8790

Example 886**N-[4-N-t-Butyloxycarbonyl-N-(1,3-dicyclohexylpropan-2-yl)aminomethyl]-2-(2-methylphenyl)-benzoyl]methionine lithium salt**

The desired compound was prepared according to the method of Example 158, followed by treatment with di-t-butyl dicarbonate, and hydrolysis. ¹H NMR (300 MHz, DMSO) δ 0.68-0.87 (m, 4H), 0.95-1.10 (m, 13H), 1.28 (s, 3H), 1.40 (s, 6H), 1.50-1.70 (m, 13H), 1.94 (s, 3H), 1.97-2.18 (m, 5H), 3.55-3.70 (m, 1H), 4.20-4.40 (m, 3H), 6.85-6.95 (m, 1H), 7.01-7.27 (m, 5H), 7.30-7.42 (m, 1H), 7.42-7.53 (m, 1H). MS (APCI(+)) m/z 679 (M+H); Analysis calc'd for C₄₀H₅₇LiN₂O₅S•0.75H₂O: C, 68.79; H, 8.44; N, 4.01; found: C, 68.77; H, 8.33; N, 4.04.

8800

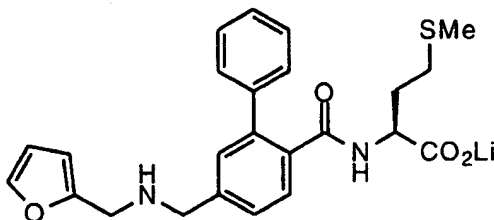


Example 887

N-[4-N-(3-Cyclohexyl-1-oxo-1-piperidin-1-yl)propan-2-yl]aminomethyl-2-(2-methylphenyl)benzoyl]-methionine lithium salt

The desired compound was prepared according to the method of Example 158. ¹H NMR (300 MHz, DMSO) δ 0.65-0.90 (m, 2H), 1.00-1.24 (m, 10H), 1.30-1.70 (m, 15H), 1.90 (s, 3H), 1.92-2.18 (m, 5H), 3.35-3.80 (m, 3H), 6.85-6.95 (m, 1H), 7.06-7.23 (m, 5H), 7.32 (d, $J=7.8$ Hz, 1H), 7.46 (d, $J=7.8$ Hz, 1H). MS (ESI(-)) m/z 592 (M-H);

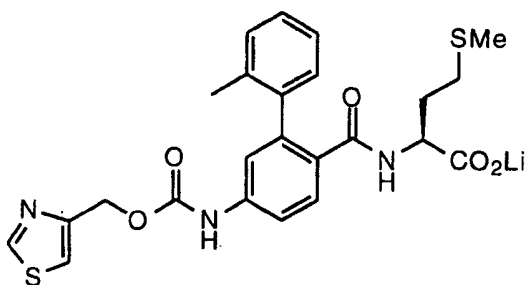
Analysis calc'd for C₃₄H₄₆LiN₃O₄S•1.30H₂O: C, 65.53; H, 7.86; N, 6.74; found: C, 65.53; H, 7.36; N, 6.41.



Example 890

N-[4-(N-(furan-2-ylmethyl)aminomethyl)-2-phenylbenzoyl]methionine lithium salt

The desired compound was prepared according to the method of Example 158. ¹H NMR (DMSO-*d*₆, 90 °C) δ 7.48-7.24 (m, 9 H), 7.07-7.04 (m, 1 H), 6.37-6.34 (m, 1 H), 6.24-6.20 (m, 1 H), 3.76-3.69 (m, 5 H), 2.43-2.16 (m, 3 H), 2.00-1.66 (m, 5 H); MS m/z 439 (M⁺ + 1, 100). Anal. Calcd for C₂₄H₂₅LiN₂O₄S•2H₂O (480.50): C, 59.99; H, 6.08; N, 5.83. Found: C, 59.83; H, 5.83; N, 5.74.

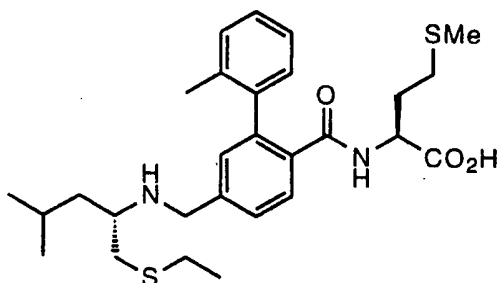


8825

Example 902N-[4-N-(thiazol-5-ylmethoxycarbonyl)amino-2-(2-methylphenyl)benzoyl]methionine lithium salt

8830

The desired compound was prepared according to the method of Example 57. ¹H NMR (DMSO-*d*₆) δ 9.93 (s, 1 H), 9.04 (s, 1 H), 7.93 (s, 1 H), 7.44 (s, 2 H), 7.19-7.06 (m, 4 H), 6.92-6.88 (m, 1 H), 6.78-6.74 (m, 1 H), 5.34 (s, 2 H), 3.61-3.56 (m, 1 H), 2.10-1.79 (m, 8 H), 1.77-1.63 (m, 1 H), 1.60-1.53 (m, 1 H); MS *m/z* 498 (M⁺ - 1, 100). Exact mass calcd for C₂₄H₂₆N₃O₅S₂ 500.1303, found 500.1308.



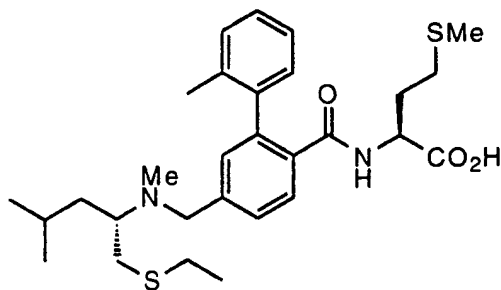
8835

Example 905N-[4-(N-(1-ethylthio-4-methylpentan-2-yl)aminomethyl)-2-(2-methylphenyl)benzoyl]methionine

8840

The desired compound was prepared according to the method of Example 158. ¹H (300MHz, CDCl₃, δ) 7.70 (1H, m), 7.43 (1H, d, *J*=10Hz), 7.30-7.00 (5H, m), 6.25 (1H, m), 4.38 (1H, m), 4.06 (1H, m), 3.91 (1H, bd, *J*=12Hz), 3.01 (1H, m), 2.82 (1H, dd, *J*=15&3Hz), 2.67 (1H, m), 2.45 (2H, q, *J*=8Hz), 2.05 (3H, s), 2.00 (3H, s), 2.00-1.80 (4H, m), 1.67 (1H, m), 1.53 (3H, m), 1.20 (3H, t, *J*=8Hz), 0.92 (3H, d, *J*=8Hz), 0.85 (3H, d, *J*=8Hz). *m/z* (ESI) 517 (MH⁺) Anal. calc. for C₂₈H₄₀N₂O₃S₂ C 65.08, H 7.80, N 5.42 Found C 65.37, H 7.86, N 5.38

8845

Example 906

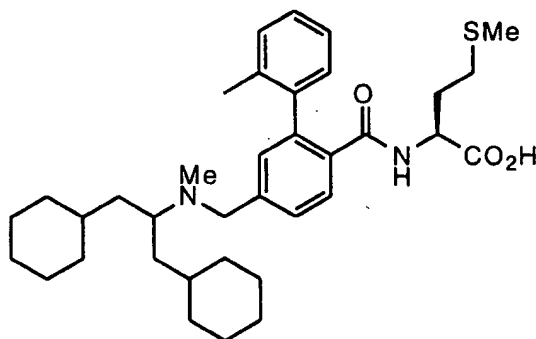
8850

N-[4-(*N*-(1-ethylthio-4-methylpentan-2-yl)-*N*-methylaminomethyl)-2-(2-methylphenyl)benzoyl]-methionine

8855

The desired compound was prepared according to the method of Example 158. ^1H (300MHz, CDCl_3 , δ) (rotamer) 7.70 (1H, m), 7.52 (1H, d, $J=10\text{Hz}$), 7.40-7.10 (5H, m), 6.08 (1H, m), 4.43 (1H, m), 3.88 (2H, m), 3.15 (1H, m), 2.87 (1H, dd, $J=15\&3\text{Hz}$), 2.60 (1H, m), 2.51 (2H, q, $J=8\text{Hz}$), 2.38 (2.36) (3H, s), 2.06 (2.13) (3H, s), 2.00 (3H, s), 2.00-1.60 (4H, m), 1.60-1.40 (3H, m), 1.22 (3H, t, $J=8\text{Hz}$), 0.92 (3H, d, $J=8\text{Hz}$), 0.88 (3H, d, $J=8\text{Hz}$). m/z (ESI) 531 (MH^+) Anal.calc. for $\text{C}_{29}\text{H}_{42}\text{N}_2\text{O}_3\text{S}_2 \cdot 0.25 \text{H}_2\text{O}$ C 65.07, H 8.00, N 5.23 Found C 65.01, H 7.84, N 5.14

8860

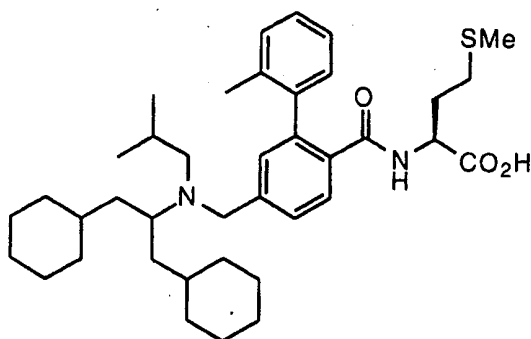
Example 907

N-[4-(*N*-(1,3-Dicyclohexylpropan-2-yl)-*N*-methylaminomethyl)-2-(2-methylphenyl)benzoyl]methionine

8865

The desired compound was prepared according to the method of Example 158. ^1H (300MHz, $\text{DMSO}-d_6$, δ) 7.50 (1H, d, $J=12\text{Hz}$), 7.33 (1H, m), 7.25-7.10 (3H, m), 7.08 (1H, m), 6.98 (1H, m), 3.82 (1H, m), 3.55 (2H, m), 2.20-2.00 (3H, m), 2.08 (3H, s), 1.93 (3H, s), 1.82 (3H, s), 1.75-1.40 (12H, m), 1.40-1.20 (5H, m), 1.20-0.90 (9H, m), 0.90-0.70 (3H, m). m/z (ESI) 593 (MH^+)

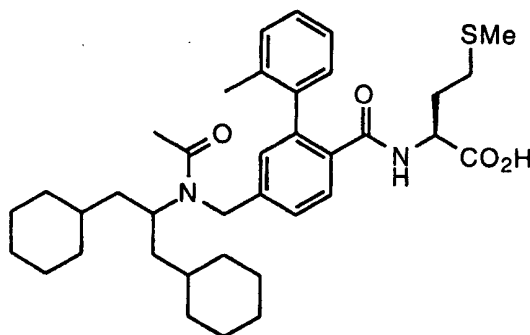
8870



Example 908

8875 N-[4-(N-(1,3-Dicyclohexylpropan-2-yl)-N-methylaminomethyl)-2-(2-methylphenyl)-
benzoyl]methionine

The desired compound was prepared according to the method of Example 158. ¹H (300MHz, DMSO-d₆, δ) (rotamer) 7.65 (1H, m), 7.49 (1H, bd, J=12Hz), 7.33 (1H, dd, J=12&2Hz), 7.30-7.00 (4H, m), 4.50 (2H, m), 4.10 (1H, m), 3.53 (1H, m), 3.20 (1H, m), 2.58 (1H, m), 2.20-2.00 (6H, m), 1.97 (1.92) (3H, s), 1.80-1.40 (14H, m), 1.40-1.20 (4H, m), 1.20-0.90 (8H, m), 0.90-0.60 (9H, d, J=9Hz). m/z (ESI) 635 (MH⁺) Anal.calc. for C₃₉H₅₈N₂O₃S·1.00 H₂O C 71.74, H 9.26, N 4.29 Found C 71.60, H 8.90, N 4.27

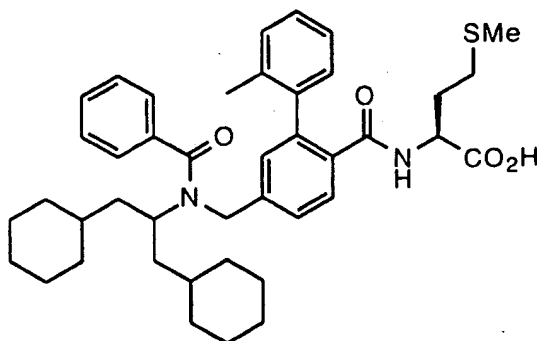


Example 909

8885 N-[4-(N-acetyl-N-(1,3-Dicyclohexylpropan-2-yl)aminomethyl)-2-(2-methylphenyl)-
benzoyl]methionine

8890 The desired compound was prepared according to the method of Example 158, followed by Schotten-Baumann acylation and subsequent hydrolysis ¹H (300MHz, DMSO-d₆, δ) (rotamer) 12.60 (1H, m), 8.05 (1H, m), 7.48 (1H, m), 7.35 (1H, bd, J=12Hz), 7.20-6.90 (4H, m), 4.50 (2H, bd, J=18Hz), 4.22 (1H, m), 3.87 (1H, m), 3.10 (1H, m), 2.20-2.00 (4H, m), 2.08 (3H, s), 1.96 (1.94) (3H, s), 1.80 (3H, m), 1.60-1.30 (9H, m), 1.30-1.00 (14H, m), 0.80-0.60 (3H, m). m/z (ESI) 621 (MH⁺) Anal.calc. for C₃₇H₅₂N₂O₄S·0.50 H₂O C 70.55, H 8.48, N 4.45 Found C 70.67, H 8.42, N 4.36

8895

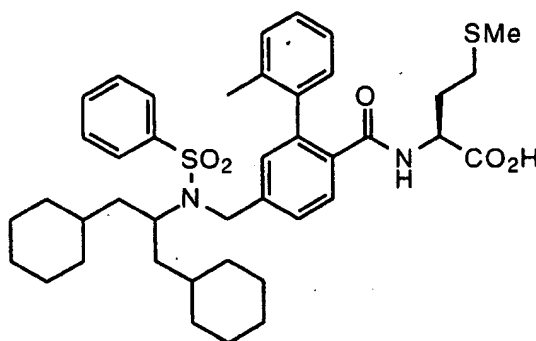
**Example 910**

N-[4-(*N*-benzoyl-*N*-(1,3-Dicyclohexylpropan-2-yl)aminomethyl)-2-(2-methylphenyl)-benzoyl]methionine

8900

The desired compound was prepared according to the method of Example 909. ^1H (300MHz, DMSO- d_6 , δ) 12.60 (1H, m), 8.05 (1H, bd, $J=12\text{Hz}$), 7.47 (4H, m), 7.33 (2H, m), 7.25-7.10 (5H, m), 4.62 (2H, bs), 4.21 (1H, m), 3.82 (1H, m), 3.10 (1H, m), 2.20-2.00 (4H, m), 1.96 (3H, s), 1.80 (3H, m), 1.60-1.30 (9H, m), 1.30-1.00 (14H, m), 0.80-0.60 (3H, m). m/z (ESI) 683 (MH^+) Anal. calc. for $\text{C}_{42}\text{H}_{54}\text{N}_2\text{O}_4\text{S} \cdot 0.75 \text{H}_2\text{O}$ C 72.43, H 8.03, N 4.02 Found C 72.24, H 7.72, N 3.93

8905

**Example 911**

N-[4-(*N*-Benzenesulfoyl-*N*-(1,3-Dicyclohexylpropan-2-yl)aminomethyl)-2-(2-methylphenyl)-benzoyl]methionine

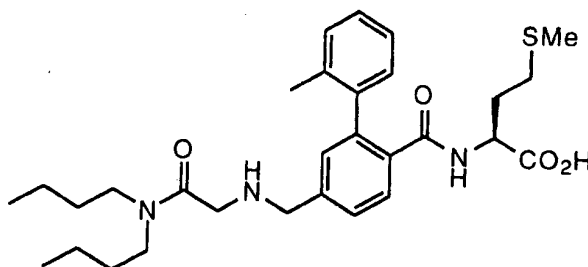
8910

The desired compound was prepared according to the method of Example 157. ^1H (300MHz, DMSO- d_6 , δ) 7.83 (2H, bd, $J=12\text{Hz}$), 7.80-7.55 (3H, m), 7.49 (2H, m), 7.30-7.00 (5H, m), 4.43 (2H, m), 4.22 (1H, m), 3.78 (1H, m), 3.20 (1H, m), 2.25-2.00 (4H, m), 1.97 (3H, s), 1.90-1.70 (3H, m), 1.60-1.40 (9H, m), 1.30-0.90 (14H, m), 0.80-0.40

8915

(3H, m). m/z (ESI) 719 (MH^+) Anal.calc. for $C_{41}H_{54}N_2O_5S_2 \cdot 0.50 H_2O$ C 67.64, H 7.61, N 3.85 Found C 67.74, H 7.48, N 3.79

8920

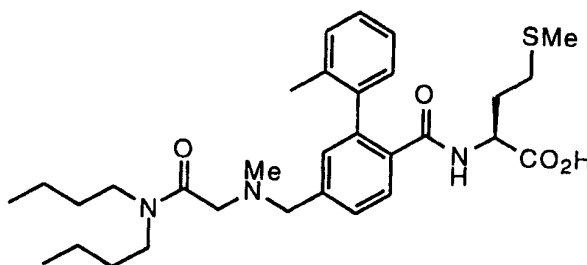


Example 912

N-[4-(N,N-dibutylacetamido)aminomethyl]-2-(2-methylphenyl)benzoyl]methionine

The desired compound was prepared according to the method of Example 158. 1H (300MHz, DMSO- d_6 , δ) 7.96 (1H, m), 7.48 (1H, d, $J=10Hz$), 7.39 (1H, dd, $J=12\&2Hz$), 7.25-7.00 (4H, m), 4.17 (1H, m), 3.80 (2H, s), 3.23 (2H, t, $J=8Hz$), 3.16 (2H, t, $J=8Hz$), 2.20-2.00 (5H, m), 1.96 (3H, s), 1.90-1.60 (2H, m), 1.41 (4H, m), 1.22 (4H, m), 0.85 (6H, q, $J=8Hz$). m/z (DCI, NH_3) 542 (MH^+) Anal.calc. for $C_{30}H_{43}N_3O_4S \cdot 0.75 H_2O$ C 64.89, H 8.08, N 7.57 Found C 64.83, H 7.94, N 7.33

8930



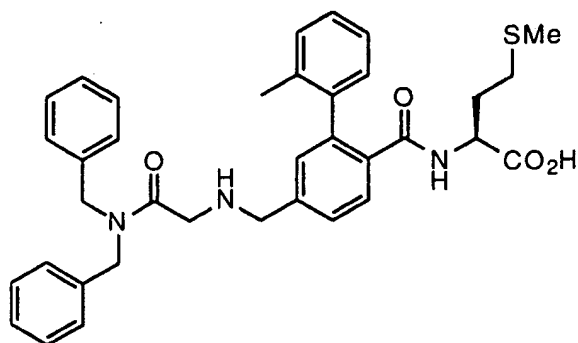
Example 913

N-[4-(N,N-dibutylacetamido)-N-methylaminomethyl]-2-(2-methylphenyl)benzoyl]methionine

8935

The desired compound was prepared according to the method of Example 158. 1H (300MHz, DMSO- d_6 , δ) 7.53 (1H, d, $J=10Hz$), 7.38 (1H, dd, $J=12\&2Hz$), 7.25-7.00 (4H, m), 4.23 (1H, m), 3.64 (2H, s), 3.48 (1H, m), 3.35-3.16 (4H, m), 3.14 (1H, m), 2.22 (3H, s), 2.20-2.00 (5H, m), 1.96 (3H, s), 1.90-1.60 (2H, m), 1.42 (4H, m), 1.19 (4H, m), 0.86 (6H, q, $J=8Hz$). m/z (ESI) 556 (MH^+) Anal.calc. for $C_{31}H_{45}N_3O_4S$ C 66.99, H 8.16, N 7.56 Found C 66.65, H 8.20, N 7.23

8940

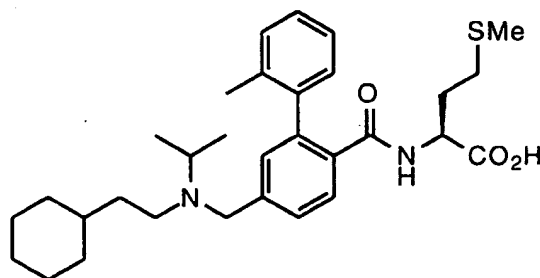


8945

Example 914N-[4-(N,N-dibenzylacetamido)aminomethyl]-2-(2-methylphenyl)benzoyl]methionine

The desired compound was prepared according to the method of Example 158. ¹H (300MHz, DMSO-d₆, δ) (rotamer) 7.76 (1H, m), 7.40 (1H, d, J=9Hz), 7.30-7.00 (15H, m), 4.41 (4H, d, J=12Hz), 4.10 (1H, m), 3.73 (2H, s), 3.41 (2H, s), 2.20-1.90 (5H, m), 1.87 (1.83) (3H, s), 1.80-1.50 (2H, m). m/z (ESI) 610 (MH⁺)

8950

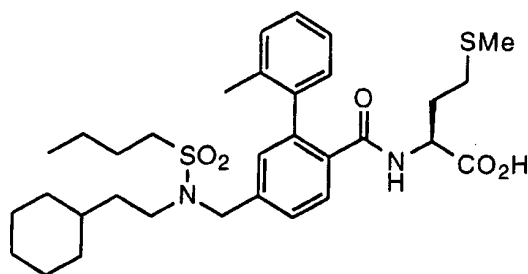
Example 915

8955

N-[4-(N-(2-Cyclohexylethyl)-N-isopropylaminomethyl)-2-(2-methylphenyl)benzoyl]methionine

The desired compound was prepared according to the method of Example 158. ¹H (300MHz, CDCl₃, δ) 7.80-7.60 (2H, m), 7.30-7.00 (5H, m), 6.50 (1H, d, J=8Hz), 4.38 (1H, m), 4.03 (2H, m), 3.67 (1H, m), 2.88 (2H, m), 2.20-2.00 (7H, m), 2.00 (3H, s), 1.80-1.40 (8H, m), 1.33 (6H, d, J=7Hz), 1.30-1.00 (3H, m), 1.00-0.80 (2H, m). m/z (ESI) 525 (MH⁺) Anal.calc. for C₃₁H₄₄N₂O₃S·0.50 H₂O C 69.76, H 8.50, N 5.25 Found C 69.90, H 8.26, N 5.57

8960

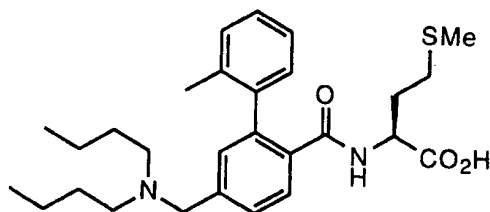


8965

Example 916N-[4-(N-Butanesulfonyl-N-(2-cyclohexylethyl)aminomethyl)-2-(2-methylphenyl)benzoyl]methionine

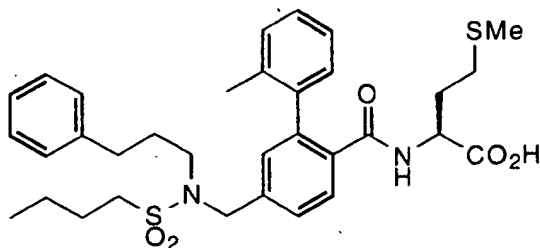
The desired compound was prepared according to the method of Example 157. ¹H (300MHz, CDCl₃, δ) 7.99 (1H, m), 7.45 (1H, dd, J=9&2Hz), 7.40-7.10 (5H, m), 5.92 (1H, m), 4.56 (1H, m), 4.44 (2H, s), 3.20 (2H, m), 2.96 (2H, m), 2.20-2.05 (5H, m), 2.02 (3H, s), 2.00-1.70 (3H, m), 1.70-1.30 (10H, m), 1.30-1.00 (4H, m), 0.95 (3H, t, J=8Hz), 0.83 (2H, m). m/z (ESI) 603 (MH⁺) Anal.calc. for C₃₂H₄₆N₂O₅S₂·0.25 H₂O C 63.28, H 7.72, N 4.61 Found C 63.27, H 7.73, N 4.50

8975

Example 917N-[4-(N,N-Dibutylaminomethyl)-2-(2-methylphenyl)benzoyl]methionine

The desired compound was prepared according to the method of Example 158. ¹H (300MHz, CDCl₃, δ) 7.75 (1H, d, J=9Hz), 7.67 (1H, m), 7.30-7.10 (5H, m), 6.33 (1H, m), 4.42 (1H, m), 4.13 (2H, m), 2.95 (4H, m), 2.20-2.00 (5H, m), 2.00 (3H, s), 2.00-1.80 (2H, m), 1.68 (4H, m), 1.33 (4H, m), 0.93 (6H, q, J=8Hz). m/z (DCI, NH₃) 485 (MH⁺) Anal.calc. for C₂₈H₄₀N₂O₃S·1.00 H₂O C 66.90, H 8.42, N 5.57 Found C 66.73, H 8.23, N 5.40

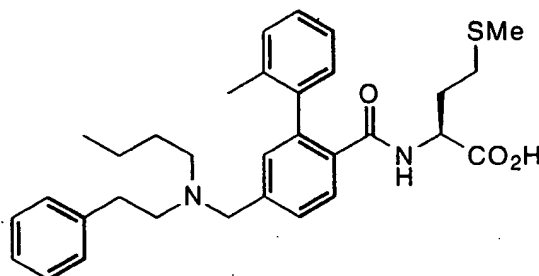
8985



Example 927

N-[4-(N-Butanesulfonyl)-N-(3-phenylpropyl)aminomethyl]-2-(2-methylphenyl)benzoyl]methionine

The desired compound was prepared according to the method of Example 157 ¹H (300MHz, CDCl₃, δ) 7.97 (1H, m), 7.40 (1H, dd, *J*=9&2Hz), 7.35-7.10 (8H, m), 7.04 (1H, d, *J*=2Hz), 7.03 (1H, s), 5.89 (1H, m), 4.60 (1H, m), 4.43 (2H, s), 3.22 (2H, t, *J*=8Hz), 2.96 (2H, t, *J*=8Hz), 2.55 (2H, t, *J*=8Hz), 2.20-2.05 (2H, m), 2.05 (3H, s), 2.02 (3H, s), 2.00-1.70 (5H, m), 1.57 (1H, m), 1.42 (2H, m), 0.94 (3H, t, *J*=8Hz). *m/z* (ESI) 609 (MH⁺) Anal.calc. for C₃₃H₄₂N₂O₅S₂ C 64.89, H 6.93, N 4.59 Found C 64.61, H 6.90, N 4.52



Example 928

N-[4-(N-Butyl)-N-(2-phenylethyl)aminomethyl]-2-(2-methylphenyl)benzoyl]methionine

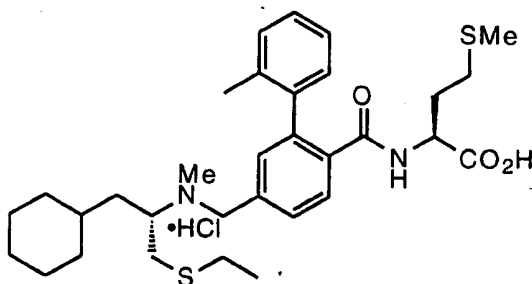
The desired compound was prepared according to the method of Example 157 ¹H (300MHz, CDCl₃, δ) 7.78 (1H, d, *J*=9Hz), 7.60 (1H, bd, *J*=8Hz), 7.40-7.20 (5H, m), 7.20-7.00 (5H, m), 6.27 (1H, m), 4.43 (1H, m), 4.20-4.00 (2H, m), 3.20-2.80 (6H, m), 2.20-2.05 (5H, m), 1.98 (3H, s), 1.90 (1H, m), 1.63 (3H, m), 1.32 (2H, m), 0.93 (3H, t, *J*=8Hz). *m/z* (ESI) 533 (MH⁺) Anal.calc. for C₃₂H₄₀N₂O₃S·1.00 H₂O C 69.79, H 7.69, N 5.09 Found C 70.04, H 7.48, N 4.96

Example 936

9015 N-[4-(N-benzylaminomethyl)-2-phenylbenzoyl]methionine hydrochloride salt

The desired compound was prepared according to the method of Example 158 (DMSO-d₆) δ 8.61 (d, 1H), 7.61 (m, 1H), 7.58 (m, 3H), 7.40 (m, 9H), 4.32 (m, 1H), 4.22 (s, 2H), 4.18 (s, 2H), 2.27 (m, 2H), 2.00 (s, 3H), 1.88 (m, 2H). MS (DCI/NH₃) 449 (M+H)⁺. Anal calcd for C₂₆H₂₉ClN₂O₃S · 0.80 H₂O: C, 62.53; H, 6.18; N, 5.61.

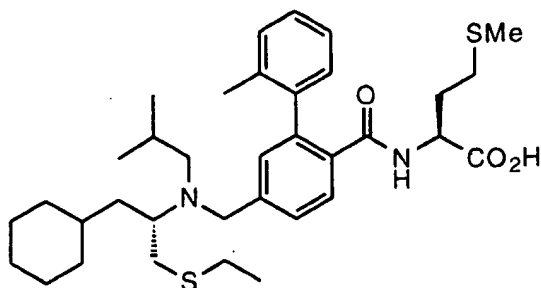
9020 Found: C, 62.59; H, 6.31; N, 5.57.

Example 944

9025 N-[4-N-(3-Cyclohexyl-1-ethylthiopropyl)-N-methylaminomethyl]-2-(2-methylphenyl)benzoyl]-methionine hydrochloride salt

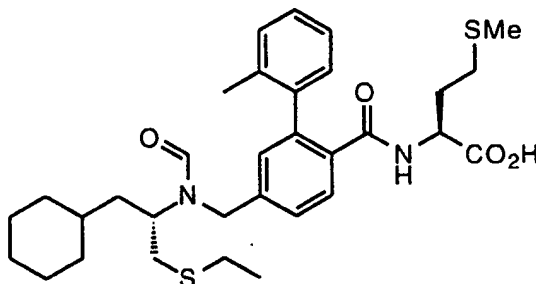
The desired compound was prepared according to the method of Example 158 (DMSO-d₆) δ 8.23 (m, 1H), 7.75 (m, 1H), 7.59, 7.50 (both m, total 2H), 7.22, 7.15 (both m, total 4H), 4.50, 4.38 (both m, total 2H), 4.22 (m, 1H), 3.10, 2.90, 2.70 (all m, total 5H), 2.40, 2.10 (both m, total 7H), 1.98 (s, 3H), 1.90-1.40 (envelope, total 10H), 1.15, 1.00, 0.82 (all m, total 7H). MS (ESI) 569 (M-H)⁻. Anal calcd for C₃₂H₄₇ClN₂O₃S₂: C, 63.29; H, 7.80; N, 4.61. Found: C, 63.07; H, 7.79; N, 4.51.

9030

**Example 945**

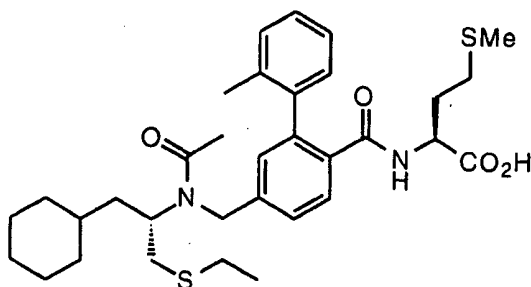
N-[4-*N*-(3-Cyclohexyl-1-ethylthiopropyl)-*N*-isobutylaminomethyl-2-(2-methylphenyl)benzoyl]-methionine

The desired compound was prepared according to the method of Example 158 (DMSO- d_6) δ 8.05 (d, 1H), 7.55 (d, 1H), 7.42 (d, 1H), 7.22, 7.20 (both m, total 5H), 4.27 (m, 1H), 3.73 (d, 1H), 3.60 (d, 1H), 2.90 (dd, 1H), 2.77 (m, 1H), 2.45 (q, 2H), 2.30, 2.10 (both m, total 8H), 2.00 (s, 3H), 1.97-1.25 (envelope, 11H), 1.19 (t, 3H), 1.19-0.70 (envelope, 12H). MS (ESI) 611 (M-H)⁻. Anal calcd for C₃₃H₅₂N₂O₃S₂ · 0.25 H₂O : C, 68.09; H, 8.57; N, 4.54. Found: C, 67.96; H, 8.53; N, 4.49.

**Example 946**

N-[4-*N*-(3-Cyclohexyl-1-ethylthiopropyl)-*N*-formylaminomethyl-2-(2-methylphenyl)benzoyl]-methionine

The desired compound was prepared according to the method of Example 607, followed by Schotten-Baumann acylation. (DMSO- d_6) δ 8.40, 8.27 (both s, total 1H), 8.03, 7.97 (both d, total 1H), 7.45 (m, 2H), 7.20, 7.15 (both m, total 5H), 4.40 (m, 2H), 4.21 (m, 1H), 3.70 (m, 1H), 2.62, 2.46 (both m, total 4H), 2.18, 2.05 (both m, total 5H), 1.96 (s, 3H), 1.90-1.20 (envelope, 9H), 1.10, 1.00, 0.75 (all m, total 9H). MS (ESI) 585 (M-H)⁻. Anal calcd for C₃₂H₄₄N₂O₄S₂ : C, 65.72; H, 7.58; N, 4.79. Found: C, 65.47; H, 7.53; N, 4.74.

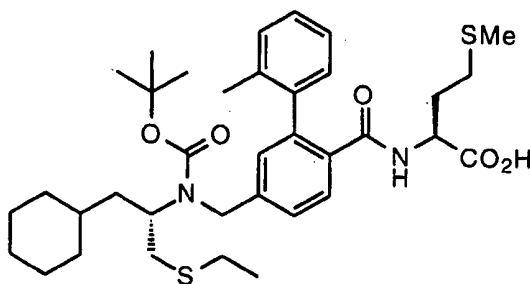


9060

Example 947*N*-[4-*N*-acetyl-*N*-(3-Cyclohexyl-1-ethylthiopropyl)aminomethyl-2-(2-methylphenyl)benzoyl]methionine

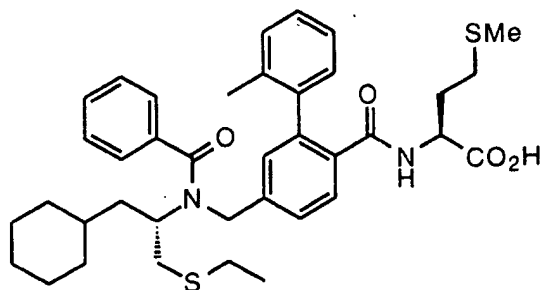
The desired compound was prepared according to the method of Example 946
 9065 (DMSO- d_6) δ 8.12, 8.00 (both d, total 1H), 7.55, 7.45, 7.40 (all m, total 2H), 7.20, 7.10, 7.06 (all m, total 5H), 4.65, 4.58 (both m, total 2H), 4.30, 4.20, 3.94 (all m, total 2H), 2.79, 2.60, 2.48 (all m, total 4H), 2.10, 1.97 (m, s, total 11H), 1.90-1.20 (envelope, 9H), 1.15, 1.10, 0.80 (all m, total 9H). MS (ESI) 597 (M-H)⁻. Anal calcd for C₃₃H₄₆N₂O₄S₂: C, 66.19; H, 7.74; N, 4.68. Found: C, 66.02; H, 7.68; N, 4.56.

9070

Example 948*N*-[4-*N*-t-Butyloxycarbonyl-*N*-(3-cyclohexyl-1-ethylthiopropyl)aminomethyl-2-(2-methylphenyl)benzoyl]methionine

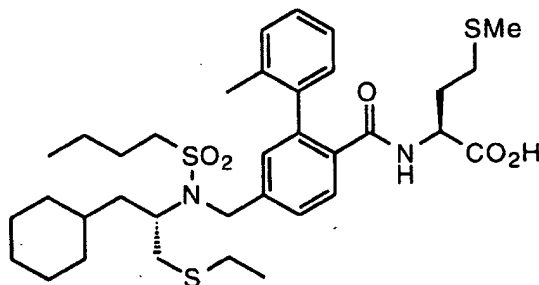
9075

The desired compound was prepared according to the method of Example 946
 9080 (DMSO- d_6) δ 7.95 (m, 1H), 7.46 (m, 1H), 7.38 (m, 1H), 7.20, 7.10 (both m, total 5H), 4.40, 4.30, 4.20 (all m, total 4H), 2.60, 2.47 (both m, total 4H), 2.10 (m, 5H), 1.97 (s, 3H), 1.90-1.00 (envelope, 25H), 0.78 (m, 2H). MS (ESI) 655 (M-H)⁻. Anal calcd for C₃₆H₅₂N₂O₅S₂: C, 65.82; H, 7.98; N, 4.26. Found: C, 65.56; H, 7.99; N, 4.20.

**Example 949**

9085 *N*-[4-*N*-Benzoyl-*N*-(3-Cyclohexyl-1-ethylthiopropyl)aminomethyl-2-(2-methylphenyl)-benzoyl]methionine

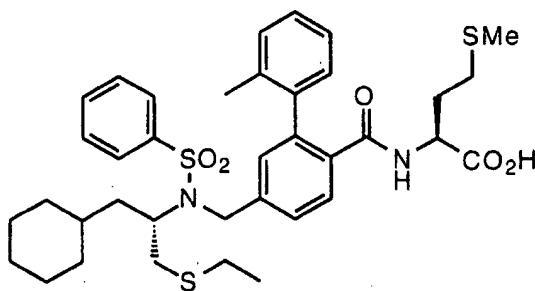
The desired compound was prepared according to the method of Example 946 (DMSO- d_6) δ 8.10 (d, 1H), 7.44 (m, 7H), 7.20 (m, 5H), 4.77, (d, 1H), 4.57 (d, 1H), 4.22 (m, 1H), 3.82 (m, 1H), 2.82 (m, 1H), 2.62 (m, 1H), 2.23, 2.10 (both m, total 7H), 1.97 (s, 3H), 1.80 (m, 2H), 1.48, 1.38 (both m, total 5H), 1.06, 0.65 (both m, total 11H). 9090 MS (ESI) 659 (M-H)⁻. Anal calcd for C₃₈H₄₈N₂O₄S₂: C, 69.06; H, 7.32; N, 4.24. Found: C, 68.94; H, 7.31; N, 4.17.

**Example 950**

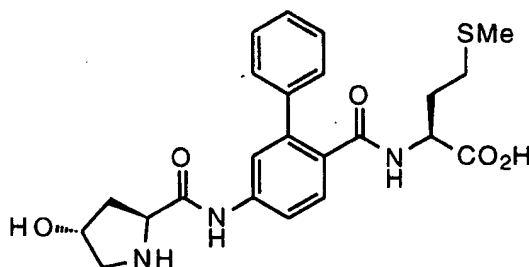
9095 *N*-[4-*N*-Butanesulfonyl-*N*-(3-Cyclohexyl-1-ethylthiopropyl)aminomethyl-2-(2-methylphenyl)-benzoyl]methionine

The desired compound was prepared according to the method of Example 157 (DMSO- d_6) δ 8.08 (d, 1H), 7.57 (s, 2H), 7.35, 7.25, 7.18 (all m, total 5H), 4.44 (m, 2H), 9100 4.28 (m, 1H), 3.87 (m, 1H), 3.10 (m, 2H), 2.77, 2.64, 2.55 (all m, total 4H), 2.10 (m, 5H), 2.00 (s, 3H), 1.95-1.50 (envelope, 8H), 1.42, 1.30, 1.20, 1.10 (m, m, t, m, total 12H), 0.90 (t, 3H), 0.80 (m, 2H). MS (ESI) 675 (M-H)⁻. Anal calcd for C₃₅H₅₂N₂O₅S₃: C, 62.10; H, 7.74; N, 4.14. Found: C, 61.86; H, 7.57; N, 4.18.

9105

**Example 951****N-[4-N-Benzenesulfonyl-N-(3-cyclohexyl-1-ethylthiopropyl)aminomethyl-2-(2-methylphenyl)-benzoyl]methionine**

The desired compound was prepared according to the method of Example 157 (DMSO- d_6) δ 8.07 (d, 1H), 7.86 (d, 2H), 7.70 (m, 1H), 7.64 (m, 2H), 7.50 (s, 2H), 7.20 (m, 5H), 4.50 (m, 2H), 4.22 (m, 1H), 3.72 (m, 1H), 2.50-2.00 (envelope, 10H), 1.98 (s, 3H), 1.80 (m, 2H), 1.42, 1.20, 1.06, 0.90, 0.63 (m, m, t, m, m, total 15H). MS (ESI) 695 (M-H)⁻. Anal calcd for C₃₇H₄₈N₂O₅S₃: C, 63.76; H, 6.94; N, 4.02. Found: C, 63.63; H, 6.93; N, 3.94.

**Example 952****N-[4-(4-hydroxyprolinylamino)-2-phenylbenzoyl]methionine****Example 952A****N-[4-N-(N-*t*-butoxycarbonyl-4-*t*-butyldimethylsilyloxy-L-prolinyl)amino-2-phenylbenzoyl]-methionine methyl ester**

To a solution of *N-t*-butoxycarbonyl-4-*t*-butyldimethylsilyloxy-L-proline methyl ester (1.3 g, 3.6 mmol) in methanol (10 mL) was added 1N LiOH (5 mL) in an ice-bath. The reaction mixture was stirred for 30 min. The reaction mixture was adjusted to pH2-3 with 1N HCl at the same temperature and the solvent was evaporated. The resulting residue was partitioned with dichloromethane and water, and extracted 3 times with dichloromethane. The combined organic solution was washed with 1N HCl and water, dried over anhydrous

magnesium sulfate, and concentrated in vacuo to give the corresponding acid **2** (1.05 g, 96 %) as a foamy solid. Without any purification, **2** (1.0 g, 3.29 mmol) was dissolved in 15 ml of dichloromethane. To this solution was added triethylamine (550 μ L, 3.9 mmol) in an ice-bath under argon, followed by IBCF (470 μ L, 3.6 mmol). The reaction mixture was allowed to stir for 40 min. At this time TLC showed the absence of the starting material. To this solution 4-amino-2-phenylbenzoyl methionine methyl ester² **3** (1.07 g, 2.97 mmol) in dichloromethane (10 mL) was introduced. The reaction mixture was stirred overnight, during which time the ice-bath expired. The reaction mixture was washed with 1N HCl, 5% sodium bicarbonate, and water, dried over magnesium sulfate, and solvent was removed. The residue was flash-chromatographed on silica gel using a 7:3 solution of hexanes and EtOAc to yield **4** (1.92 g, 94 %) as a foamy solid: mp 83°C; $[\alpha]^{25}_{\text{D}} -36.2$ ($c=0.63$, CHCl_3); ^1H NMR (300 MHz, CDCl_3) δ 9.94 (s, 1H), 7.53-7.26 (m, 8H), 6.41 (d, 1H, $J=6.0\text{Hz}$), 4.55 (m, 4H), 3.63 (s, 3H), 3.57 (m, 1H), 3.32 (m, 1H), 2.30 (m, 1H), 2.05 (m, 2H), 1.94 (s, 3H), 1.83 (m, 1H), 1.73 (m, 1H), 1.45 (s, 9H), 0.86 (s, 9H), 0.05 (s, 6H); ^{13}C NMR (CDCl_3) δ 171.8, 170.7, 169.3, 155.6, 140.0, 129.7, 129.0, 128.5, 128.2, 127.4, 120.2, 117.7, 80.7, 77.2, 70.1, 59.5, 54.7, 52.1, 51.7, 38.0, 30.9, 29.5, 28.2, 25.5, 17.7, 15.1, 4.9; HRMS (EI) calculated for $\text{C}_{35}\text{H}_{51}\text{N}_3\text{O}_7\text{SSi}$: 685.9498, found: 685.3217. ^1H NMR (300 MHz, $\text{CDCl}_3+\text{CD}_3\text{OD}$) δ 7.53-7.29 (m, 8H), 4.67 (m, 1H), 4.58 (s, 1H), 4.50 (m, 1H), 2.57 (m, 1H), 2.14 (m, 2H), 2.01 (s, 3H), 1.96 (m, 1H), 1.76 (m, 1H); ^{13}C NMR (CD_3OD) δ 174.8, 172.6, 168.1, 142.4, 141.2, 140.6, 133.2, 130.0, 129.6, 129.5, 128.8, 122.2, 119.3, 71.2, 60.6, 55.2, 52.9, 39.9, 31.4, 30.9, 15.0.

Example 952B

9155 *N*-[4-*N*-(*N*-*t*-butoxycarbonyl)-4-hydroxy-*L*-prolinyl]amino-2-phenylbenzoyl]methionine methyl ester

To a solution of the above compound (1.82 g, 2.65 mmol) in THF (20 mL) was added 1M TBAF (3 mL). The reaction mixture was stirred for overnight, diluted with EtOAc, and washed 3 times with water. The combined aqueous washings were extracted 3 times with EtOAc. The combined organic fractions were dried over magnesium sulfate, and concentrated in vacuo. The crude product was purified by flash chromatography on silica gel using ethyl acetate as an eluent to obtain **5** (864 mg, 57%) as a white solid: mp 121-123°C; $[\alpha]^{25}_{\text{D}} -53.3$ ($c=0.43$, CHCl_3); ^1H NMR (300 MHz, CDCl_3) δ 9.84 (s, 1H), 7.60-7.38 (m, 8H), 6.35 (br s, 1H), 4.58-4.51 (br s, 4H), 3.64 (s, 3H), 3.57 (m, 1H), 3.48 (m, 1H), 2.63 (m, 1H), 2.44 (br s, 1H), 2.07 (m, 2H), 1.98 (s, 3H), 1.86 (m, 1H), 1.72 (m, 1H), 1.44 (s, 9H); HRMS (EI) calculated for $\text{C}_{29}\text{H}_{37}\text{N}_3\text{O}_7\text{S}$: 571.6872, found: 571.2352.

Example 952C

N-[4-*N*-(4-hydroxy-L-prolinyl)amino-2-phenylbenzoyl]methionine trifluoroacetate (FTI-2103)

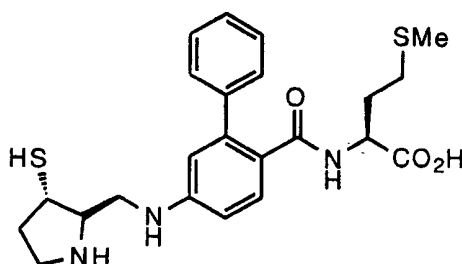
9170

9175

9180

9185

To a solution of the above compound (358 mg, 0.62 mmol) in methanol (6 mL) was added 1N LiOH (1 mL) in an ice bath. The reaction mixture was stirred for 4 hr. The reaction mixture was adjusted to pH=2-3 with 1N HCl at the same temperature and the solvent was evaporated. The resulting residue was partitioned with chloroform and water, and extracted 3 times with chloroform. The combined organic solution was washed with 1N HCl and water, dried over anhydrous magnesium sulfate, and concentrated in vacuo to give the resulting free acid (317 mg, 92 %) as a white solid. To a 5 ml of 1:1 solution of TFA and dichloromethane was added the acid (306 mg, 0.54 mmol). After 3 h, The reaction mixture was thoroughly evaporated in high vacuum to give an oily residue. The residue was triturate with anhydrous ether and the white solid was collected by filtration to give **6** (254 mg, 72%): HPLC 90% (purity); mp 127 (sub.), 154-157 °C (dec.); ¹H NMR (300 MHz, CDCl₃+CD₃OD) δ 7.53-7.29 (m, 8H), 4.67 (m, 1H), 4.58 (s, 1H), 4.50 (m, 1H), 2.57 (m, 1H), 2.14 (m, 2H), 2.01 (s, 3H), 1.96 (m, 1H), 1.76 (m, 1H); ¹³C NMR (CD₃OD) δ 174.8, 172.6, 168.1, 142.4, 141.2, 140.6, 133.2, 130.0, 129.6, 129.5, 128.8, 122.2, 119.3, 71.2, 60.6, 55.2, 52.9, 39.9, 31.4, 30.9, 15.0.



Example 959

9190

N-[4-((2S,4S)-4-thiolpyrrolidin-2-yl)methylamino)-2-phenylbenzoyl]methionine

Example 959A

N-[4-*N*-((2R,3R)-1-*t*-butyloxycarbonyl-3-*t*-butyldimethylsilyloxypyrrolidin-2-yl)methylamino)-2-phenylbenzoyl]methionine methyl ester

9195

To a solution of *N*-[4-amino-2-phenylbenzoyl]methionine methyl ester (238 mg, 0.66 mmol) and (2R,3R)-1-*t*-butyloxycarbonyl-3-*t*-butyldimethylsilyloxypyrrolidine-2-carboxaldehyde (158 mg, 0.48 mmol) in methanol (5 mL) was added acetic acid (0.5 mL), followed by sodium cyanoborohydride (65 mg, 1 mmol). The reaction mixture stirred overnight. After removal of the solvent, the residue was partitioned with ethyl acetate and 5%

9200 sodium bicarbonate, and extracted 3 times with ethyl acetate. The combined organic solution was washed with water and brine, dried over magnesium sulfate, and the solvent was removed. The residue was flash-chromatographed on silica gel using a 7:3 solution of hexanes and ethyl acetate to yield the title compound (284 mg, 88 %) as a white solid: ¹H NMR (300 MHz, CDCl₃) δ 7.68 (d, 1H, *J*=8.4 Hz), 7.40 (m, 6H), 6.62 (d, 1H), 6.44 (br s, 1H), 5.65 (d, 1H), 5.43 (s, 1H), 4.61 (m, 1H), 4.41 (br s, 1H), 4.08 (br s, 1H), 3.64 (s, 3H), 3.58-3.14 (m, 5H), 2.10 (t, 2H, *J*=7.7 Hz), 2.01 (s, 3H), 1.88 (m, 1H), 1.64 (m, 1H), 1.43 (s, 9H); 0.88 (s, 9H), 0.07 (s, 6H); HRMS (EI) calculated for C₃₅H₅₃N₃O₆SSi: 671.3424, found: 671.3415.

9210

Example 959B*N*-[4-*N*-((2R,3R)-1-*t*-butyloxycarbonyl-3-hydroxypyrrolidin-2-yl)methylamino)-2-phenylbenzoyl]methionine methyl ester

9215

9220

To a solution of the compound prepared in Example 959A (98 mg, 0.14 mmol) in THF (2 mL) was added 1M TBAF-THF (0.18 mL). The reaction mixture was stirred for 15 min at 0°C, diluted with ethyl acetate, and washed 3 times with water. The combined aqueous washings were extracted 3 times with ethyl acetate. The combined organic fractions were dried over magnesium sulfate, and concentrated in vacuo. The crude product was purified by flash chromatography on silica gel using a 3:1 solution of ethyl acetate and hexanes to obtain the title compound (60 mg, 76.8 %) as a white solid: mp 67 °C; [α]_D²⁵ +6.32 (*c*=0.19, CHCl₃); ¹H NMR (300 MHz, CDCl₃) δ 7.61 (d, 1H, *J*=8.3 Hz), 7.30 (m, 6H), 6.59 (dd, 1H, *J*=1.2, 8.3 Hz), 6.43 (d, 1H, *J*=2.1 Hz), 5.74 (d, 1H, *J*=7.6 Hz), 5.44 (br s, 1H), 4.57 (m, 1H), 4.40 (m, 1H), 4.07 (br s, 2H), 3.59 (s, 3H), 3.37-3.16 (m, 5H), 2.04 (m, 2H), 1.96 (s, 3H), 1.87 (m, 1H), 1.65 (m, 1H), 1.43 (s, 9H); HRMS (EI) calculated for C₂₉H₃₉N₃O₆S: 557.2559, found: 557.2544.

9225

Example 959C*N*-[4-*N*-((2R,3S)-1-*t*-butyloxycarbonyl-3-acetylthiopyrrolidin-2-yl)methylamino)-2-phenylbenzoyl]methionine methyl ester

9230

9235

To a solution of the compound prepared in Example 959B (300 mg, 0.53 mmol) in THF (10 mL) were added TPP (278 mg, 1.06 mmol), followed by DIAD (208 μL, 1.06 mmol) at 0°C under argon. The mixture was allowed to stir for 30 min and thiolacetic acid (76 μL, 1.06 mmol) was added to this mixture at the same temperature. The reaction mixture was stirred overnight, during which time the ice-bath expired. The solution was concentrated. The crude products were chromatographed on silica gel using a 1:1 solution of hexanes and ethyl acetate to give the desired compound (211 mg, 64 %): ¹H NMR (300 MHz, CDCl₃) δ 7.68 (d, 1H, *J*=8.2 Hz), 7.39 (m, 6H), 6.64 (br s, 1H), 6.44 (br s, 1H),

5.66 (d, 1H, $J=7.4$ Hz), 5.39 (br s, 1H), 4.60 (m, 1H), 4.03-3.87 (m, 2H), 3.62 (s, 3H), 3.42-3.11 (m, 5H), 2.33 (s, 3H), 2.07 (t, 2H, $J=7.6$ Hz), 1.99 (s, 3H), 1.87 (m, 1H), 1.64 (m, 1H), 1.43 (s, 9H); HRMS (EI) calculated for $C_{31}H_{41}N_3O_6S_2$: 615.2436, found: 615.2437.

Example 959D

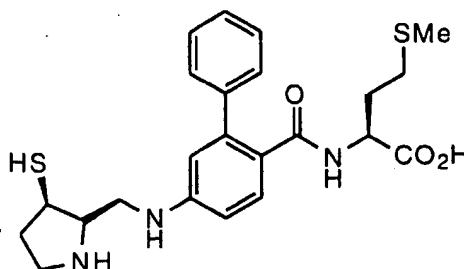
N-[4-*N*-((2*R*,3*S*)-3-acetylthiopyrrolidin-2-yl)methylamino)-2-phenylbenzoyl]methionine hydrobromide

To a solution of the compound prepared in Example 959C (106 mg, 0.17 mmol) in dichloromethane (10 mL) was added 1M boron tribromide-dichloromethane (2.58 mL) at 0° C under argon. The mixture was allowed to stir for 1 hr at the same temperature. Additionally the reaction mixture was stirred 4 hr at room temperature, and quenched by dropwise addition of water (5 mL). The solvent was removed to give crude residue. The residue was taken up with a 1:1 solution (1 mL) of water and THF, and purified by Prep-HPLC to give the desired 11 (83 mg, 73.7 %) as a white powder: 1H NMR (300 MHz, CD_3OD) δ 7.48-7.35 (m, 6H), 7.01 (d, 1H, $J=8.6$ Hz), 6.64 (s, 1H), 4.45 (dd, 1H, $J=4.1$, 9.2 Hz), 3.92-3.81 (m, 2H), 3.69-3.65 (m, 1H), 3.55-3.40 (m, 4H), 2.55 (m, 1H), 2.32 (s, 3H), 2.22 (m, 1H), 2.09 (m, 1H), 2.05 (s, 3H), 1.97 (m, 1H), 1.79 (m, 1H).

Example 959E

N-[4-((2*S*,4*S*)-4-thiolpyrrolidin-2-yl)methylamino)-2-phenylbenzoyl]methionine

To a solution of the compound described in Example 959D (80 mg, 0.12 mmol) in TFA (2 mL) was added mercuric acetate (0.38 g, 1.2 mmol) at 0° C under argon. The reaction mixture was allowed to stir for 30 min at the same temperature. This solution was evaporated and the resulting solid was suspended in methanol (10 mL). Gaseous hydrogen sulfide was bubbled into the reaction mixture for 15 min. The black precipitate was removed by filtration. After removing methanol, the residue was taken up with a 1:1 solution (1 mL) of water and THF, and purified by Prep-HPLC to afford the desired 12 (7.7 mg, 10.3 %) as a white powder: 1H NMR (300 MHz, CD_3OD) δ 7.45-7.39 (m, 6H), 6.74 (br s, 1H), 6.70 (br s, 1H), 4.44 (br s, 1H), 3.72-3.30 (m, 7H), 2.56 (br s, 1H), 2.18 (m, 1H), 2.02-1.96 (m, 2H), 2.01 (s, 3H), 1.80 (m, 1H).



9270

Example 960N-[4-((2S,4R)-4-thiolpyrrolidin-2-yl)methylamino)-2-phenylbenzoyl]methionineExample 960A

9275

(2R,3S)-1-Boc-2-*t*-butyldimethylsilyloxymethyl-3-benzoyloxypyrrolidine

To a solution of (2R,3S)-1-Boc-2-*t*-butyldimethylsilyloxymethyl-3-hydroxypyrrolidine (1.52 g, 4.59 mmol) in THF (20 mL) was added TPP (2.41 g, 9.2 mmol), followed by dropwise addition of DIAD (1.82 mL, 9.2 mmol) in THF (10 mL) at 0°C under argon atmosphere. The mixture was allowed for 40 min and benzoic acid (1.12 g, 9.2 mmol) was added dropwisely to this mixture at the same temperature. The reaction mixture was stirred overnight, during which time the ice bath expired. The solvent was removed, and a 3:1 solution of hexanes and ethyl acetate was introduced to the resulting residue to precipitate the insoluble by-products. After removal of by-products, the solution was concentrated. The crude product was chromatographed on silica gel using a 9:1 solution of hexanes and ethyl acetate to yield 14 (1.3 g, 65 %) as a foamy solid: ¹H NMR (300 MHz, CDCl₃) δ 7.55-7.32 (m, 5H), 5.49 (dd, 1H, *J* = 4.2, 11.7 Hz), 3.98-3.52 (m, 5H), 2.40 (m, 1H), 2.07 (m, 1H), 1.47 (s, 9H), 0.89 (s, 9H), 0.05 (s, 6H); MS (EI) *m/z* (relative intensity) 379 ([M-C₄H₈]⁺, 15), 322 (50), 154 (50), 105 (90), 77 (80).

9290

Example 960B(2R,3S) 1-Boc-2-*t*-butyldimethylsilyloxymethyl-3-hydroxypyrrolidine

To a solution of the compound prepared in Example 960A (1.25 g, 2.86 mmol) in methanol (5 mL) was added 1N LiOH (3 mL) in an ice-bath. The reaction mixture was stirred for 2 hr. The reaction mixture was adjusted to pH2-3 with 1N HCl at the same temperature and the solvent was evaporated. The resulting residue was partitioned with dichloromethane and water, and extracted 3 times with dichloromethane. The combined organic fractions were dried over magnesium sulfate, and concentrated in vacuo. The crude product was purified by flash chromatography on silica gel using a 3:1 solution of hexanes and ethyl acetate to obtain the desired compound (275 mg, 30%) as a white solid: mp 118°C; [α]_D²² -46.7 (*c*=0.47, CHCl₃); ¹H NMR (300 MHz, CDCl₃) δ 4.34 (s, 1H), 3.77 (dd, 1H,

9300

$J = 3.0, 9.8$ Hz), 3.66-3.29 (m, 4H), 2.54 (d, 1H, $J = 8.5$ Hz), 2.09 (m, 1H), 1.79 (m, 1H), 1.42 (s, 9H), 0.85 (s, 9H), 0.01 (s, 6H); ^{13}C NMR (CDCl_3 , minor isomer) δ 154.8, 79.7 (79.3), 74.6 (74.1), 67.0 (67.1), 63.2 (62.5), 44.7 (45.2), 31.7 (32.5), 28.7, 26.0, 18.3, -5.2; MS (EI) m/z (relative intensity) 275 ($[\text{M}-\text{C}_4\text{H}_8]^+$, 20), 259 (85), 218 (100), 86 (40), 75 (55), 57 (90).

Example 960C

(2R,3S) 1-Boc-2-*t*-butyldimethylsilyloxymethyl-3-*t*-butyldimethylsilyloxypyrrolidine

To a solution of the compound prepared in Example 960B (198 mg, 0.59 mmol) in dry DMF (2 mL) were added *tert*-butyldimethylsilyl chloride (110 mg, 0.71 mmol) and imidazole (102 mg, 1.5 mmol). The reaction mixture was stirred for 5 hr and then diluted with ether (20 mL). The reaction mixture was washed with brine, 1M HCl, and 5 % sodium bicarbonate. The organic layer was dried over magnesium sulfate, and concentrated in vacuo. The crude product was purified by flash chromatography on silica gel using a 9:1 solution of hexanes and ethyl acetate to obtain the title compound (235 mg, 88%): ^1H NMR (300 MHz, CDCl_3) δ 4.27 (m, 1H), 3.62-3.20 (m, 5H), 1.88 (m, 1H), 1.62 (m, 1H), 1.36 (s, 9H), 0.78 (s, 18H), -0.03 (s, 12H); MS (CI, isobutane) m/z (relative intensity) 446 ($[\text{M}+\text{H}]^+$, 60), 390 (10), 346 (100).

Example 960D

(2R,3S) 1-Boc-2-hydroxymethyl-3-*t*-butyldimethylsilyloxypyrrolidine

To a solution of the compound prepared in Example 960C (229 mg, 0.51 mmol) in THF (2 mL) at 0°C were added water (2 mL) and acetic acid (6 mL). The reaction mixture was stirred for overnight at room temperature. After this time, the reaction mixture was concentrated under reduced pressure. The excess water was removed by azeotrope with toluene. The crude product was purified by flash chromatography on silica gel using a 9:1 solution of hexanes and ethyl acetate to obtain the title compound (96 mg, 56.8%): ^1H NMR (300 MHz, CDCl_3) δ 4.41 (br s, 1H), 4.00 (s, 1H), 3.66-3.27 (m, 5H), 1.88 (m, 1H), 1.70 (m, 1H), 1.42 (s, 9H), 0.83 (s, 9H), 0.03 (s, 6H).

Example 960E

N-4-[(2R,3S) 1-Boc-3-*t*-butyldimethylsilyloxypyrrolidin-2-ylmethyl]amino)-2-phenylbenzoyl]methionine methyl ester

To a solution of DMSO (42 μL , 0.58 mmol) in dichloromethane (2 mL) were added trifluoroacetic anhydride (62 μL , 0.43 mmol) via syringe at -78°C under the slight stream of argon. After 10 min, the compound prepared in Example 960D (96 mg, 0.29 mmol) in dichloromethane (2 mL) was added to this mixture at the same temperature. The reaction

mixture was stirred for 1 hr. To this solution was added triethylamine (122 μ l, 0.87 mmol). The reaction mixture was allowed for 1 hr at -78°C , slowly warmed to room temperature and concentrated. After usual work-up, the crude aldehyde was used for the next step without purification. To a solution of N-[4-amino-2-phenylbenzoyl]methionine methyl ester hydrochloride (172 mg, 0.29 mmol) and the aldehyde in methanol (5 mL) were added acetic acid (0.5 mL), followed by sodium cyanoborohydride (38 mg, 0.58 mmol). The reaction mixture was allowed to react for overnight. After removal of the solvent, the residue was partitioned with ethyl acetate and 5% sodium bicarbonate, and extracted 3 times with ethyl acetate. The combined organic solution was washed with water and brine, dried over magnesium sulfate, and the solvent was removed. The residue was flash-chromatographed on silica gel using a 1:1 solution of hexanes and ethyl acetate to yield the title compound (142 mg, 73 %) as a oily residue: ^1H NMR (300 MHz, CDCl_3) δ 7.64 (d, 1H, $J=8.0$ Hz), 7.35 (m, 6H), 6.55 (d, 1H, $J=8.2$ Hz), 6.37 (br s, 1H), 5.67 (d, 1H, $J=7.6$ Hz), 5.55 (s, 1H), 4.56 (m, 1H), 4.21-3.15 (m, 7H), 3.59 (s, 3H), 2.04 (t, 2H, $J=7.7$ Hz), 1.95 (s, 3H), 1.83 (m, 1H), 1.60 (m, 1H), 1.42 (s, 9H); 0.82 (s, 9H), -0.03 (s, 6H); ^{13}C NMR (CDCl_3 , minor isomer) δ 172.1, 168.6, 156.6, 155.0, 150.1 (149.6), 147.7 (141.4), 131.4, 128.8 (128.6), 127.7, 122.6 (122.5), 113.5 (113.7), 110.9, 79.9 (80.2), 74.5, 64.9 (64.7), 60.4, 52.3, 51.8, 47.6, 45.2 (44.8), 33.1, 31.6 (31.9), 29.5, 28.4, 25.7, 21.0, 18.0, 15.3, 14.2, -4.6.

Example 960F

N-4-[(2R,3S) 1-Boc-3-hydroxypyrrolidin-2-ylmethylamino]-2-phenylbenzoyl]methionine methyl ester

To a solution of the compound prepared in Example 960E (140 mg, 0.20 mmol) in THF (3 mL) was added 1M TBAF-THF (0.3 mL). The reaction mixture was stirred for 30 min at 0°C and then quenched with saturated ammonium chloride. The reaction mixture was diluted with ethyl acetate, and washed 3 times with water. The combined aqueous washings were extracted 3 times with ethyl acetate. The combined organic fractions were dried over magnesium sulfate, and concentrated in vacuo. The crude product was purified by flash chromatography on silica gel using a 1:1 solution of ethyl acetate and hexanes to obtain the desired compound (85 mg, 76 %) as a oily residue: ^1H NMR (300 MHz, CDCl_3) δ 7.55 (d, 1H, $J=8.3$ Hz), 7.30 (m, 6H), 6.45 (d, 1H, $J=8.5$ Hz), 6.31 (br s, 1H), 5.75 (br s, 1H), 5.54 (br s, 1H), 4.51 (m, 1H), 4.15-3.82 (m, 3H), 3.56 (s, 3H), 3.59-2.98 (m, 5H), 2.00 (m, 2H), 1.92 (s, 3H), 1.80 (m, 1H), 1.56 (m, 1H), 1.38 (s, 9H).

Example 960G

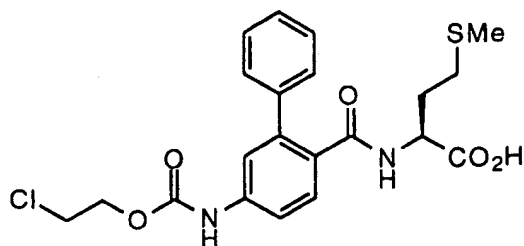
N-4-[(2R,3R) 1-Boc-3-acetylthiopyrrolidin-2-ylmethylamino]-2-phenylbenzoyl]methionine
methyl ester

To a solution of the compound prepared in Example 960F (85 mg, 0.15 mmol) in THF (3 mL) were added TPP (80 mg, 0.30 mmol), followed by DIAD (60 μ L, 0.30 mmol) at 0° C under argon. The mixture was allowed to stir for 30 min and thiolacetic acid (22 μ L, 0.31 mmol) was added to this mixture at the same temperature. The reaction mixture was stirred overnight, during which time the ice-bath expired. The solution was concentrated. The crude products were chromatographed on silica gel using a 1:1 solution of hexanes and ethyl acetate to give the desired compound (80 mg, 86.6 %) as a oily residue: ¹H NMR (300 MHz, CDCl₃) δ 7.65 (d, 1H, *J*=9.0 Hz), 7.37 (s, 5H), 6.55 (d, 1H, *J*= 7.7 Hz), 6.37 (s, 1H), 5.66 (d, 1H, *J*=7.3 Hz), 5.44 (br s, 1H), 4.58 (m, 1H), 4.40-3.98 (m, 3H), 3.60 (s, 3H), 3.38-3.06 (m, 3H), 2.32 (s, 3H), 2.21 (m, 1H), 2.07 (t, 2H, *J*=7.6 Hz), 1.99 (s, 3H), 1.87 (m, 1H), 1.64 (m, 1H), 1.43 (s, 9H); ¹³C NMR (CDCl₃) δ 194.4, 172.2, 168.5, 156.0, 150.1, 141.8, 141.4, 131.4, 128.8, 128.7, 127.8, 122.2, 113.4, 111.0, 80.5, 60.4, 57.6, 52.4, 51.8, 46.3, 45.1, 44.8, 42.3, 31.7, 30.7, 29.5, 28.4, 15.3, 14.7; HRMS (EI) calculated for C₃₁H₄₁N₃O₆S₂: 615.2436, found: 615.2436.

Example 960H

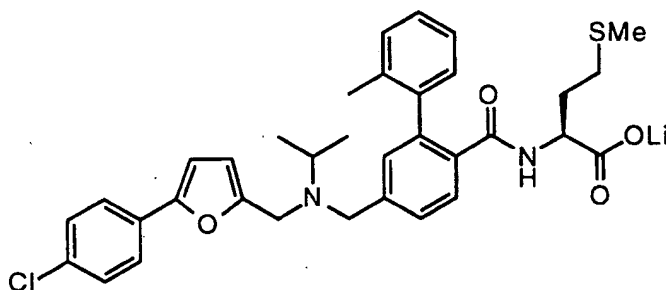
N-4-[(2R,3R) 3-thiopyrrolidin-2-ylmethylamino]-2-phenylbenzoyl]methionine
hydrobromide

To a solution of the compound prepared in Example 960G (78 mg, 0.12 mmol) in dichloromethane (5 mL) was added 1M boron tribromide-dichloromethane (1.2 mL) at 0° C under argon. The mixture was allowed to stir for 1 hr at the same temperature. Additionally the reaction mixture was stirred 4 hr at room temperature, and quenched by dropwise addition of water (5 mL). The solvent was removed to give crude residue. Without purification, the crude thioacetate was dissolved in TFA (2 mL). To this solution, mercuric acetate (0.1 g, 0.31 mmol) was added at 0° C under argon. The reaction mixture was allowed to stir for 30 min at the same temperature. This solution was evaporated and the resulting solid was suspended in methanol (10 mL). Gaseous hydrogen sulfide was bubbled into the reaction mixture for 5 min. The black precipitate was removed by filtration. After removing methanol, the residue was taken up with a 1:1 solution (1 mL) of water and THF, and purified by Prep-HPLC to afford the desired compound (17 mg, 23 %) as a white powder: ¹H NMR (300 MHz, CD₃OD) δ 7.46-7.34 (m, 6H), 6.74 (m, 1H), 6.66 (s, 1H), 4.46 (m, 1H), 4.10-3.91 (m, 2H), 3.75-3.31 (m, 4H), 2.56-2.40 (m, 2H), 2.20-1.78 (m, 4H), 2.01 (s, 3H).

Example 979N-[4-(N-2-chloroethoxycarbonyl)amino-2-phenylbenzoyl]methionine

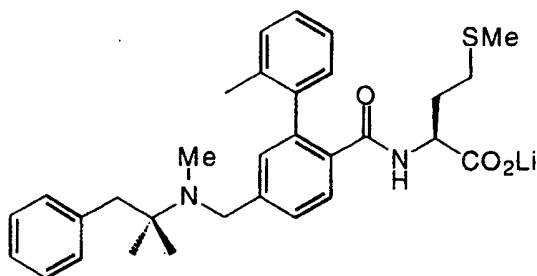
The desired compound was prepared according to the method of Example 57 ¹H
 9415 NMR (CD₃OD): δ 1.68-1.82 (m, 1 H), 1.86-2.03 (comp, 4 H), 2.03-2.26 (comp, 2 H),
 3.28 (m, 2 H), 3.72 (t, J = 5.8 Hz, 2 H), 4.44 (dd, J = 4.4, 9.2 Hz, 1 H); 6.58 (d, J = 2.3
 Hz, 1 H), 6.66 (dd, J = 2.3, 8.5 Hz, 1 H), 7.27-7.46 (comp, 8 H). LRMS (CI): 389 (M-
 62, loss of COCl)⁺.

9420

Example 980N-[4-(N-5-(4-Chlorophenyl)furan-2-ylmethyl-N-isopropylaminomethyl)-2-(2-methylphenyl)benzoyl]methionine lithium salt

The desired compound was prepared according to the method of Example 158 ¹H
 9425 NMR (300 MHz, d₆ DMSO) δ 7.59 - 7.55 (m, 2H), 7.44 (d, 1H), 7.42 - 7.36 (m, 3H),
 7.24 - 7.06 (m, 5H), 6.88 (d, 1H), 6.36 (d, 1H), 3.69 (s, 2H), 3.65 (s, 2H), 2.96 (m,
 1H), 2.16 - 1.50 (m, 11H) 1.04 (d, 6H) Calcd for the acid C₃₄H₃₆O₄N₂SCl APCI -Q1MS,
 MH- 603.

9430

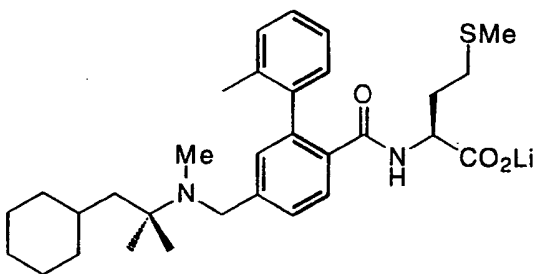
**Example 982**

N-[4-(N-Methyl-N-(1,1-dimethyl-2-phenylethyl)aminomethyl)-2-(2-methylphenyl)-benzoyl]methionine lithium salt

9435

The desired compound was prepared according to the method of Example 158 ¹H NMR (300 MHz, DMSO) δ 1.02 (s, 6H), 1.52-1.76 (m, 4H), 1.94 (s, 3H), 1.96-2.04 (m, 3H), 2.17 (s, 3H), 2.78 (s, 2H), 3.64-3.73 (m, 3H), 6.92 (d, J=5.0 Hz, 1H), 7.05-7.23 (m, 10H), 7.34 (dd, J=7.8, 1.5 Hz, 1H), 7.47 (d, J=7.8 Hz, 1H). MS (APCI(+)) *m/z* 518 (M+H); Analysis calc'd for C₃₁H₃₇LiN₂O₃S+0.85H₂O: C, 68.96; H, 7.22; N, 5.19; found: C, 68.86; H, 6.60; N, 5.25.

9440

**Example 983**

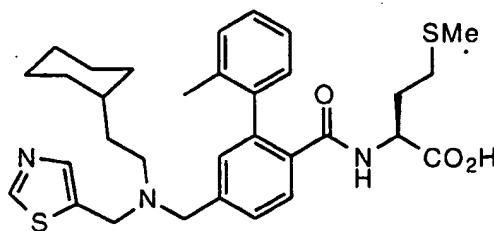
N-[4-(N-Methyl-N-(1,1-dimethyl-2-cyclohexylethyl)aminomethyl)-2-(2-methylphenyl)-benzoyl]methionine lithium salt

9445

The desired compound was prepared according to the method of Example 158 ¹H NMR (300 MHz, DMSO) δ 0.85-1.17 (m, 6H), 1.03 (brs, 6H), 1.30-1.35 (m, 2H), 1.51-1.77 (m, 10H), 1.93 (s, 3H), 1.97-2.18 (m, 3H), 2.02 (s, 3H), 3.56 (brs, 2H), 3.59-3.74 (m, 1H), 6.92 (d, J=5.0 Hz, 1H), 7.11-7.23 (m, 5H), 7.34 (d, J=7.7 Hz, 1H), 7.46 (d, J=7.8 Hz, 1H). MS (APCI(+)) *m/z* 525 (M+H); Analysis calc'd for C₃₁H₄₃LiN₂O₃S+0.80H₂O: C, 68.31; H, 8.25; N, 5.14; found: C, 68.29; H, 8.23; N, 5.04.

9450

9455

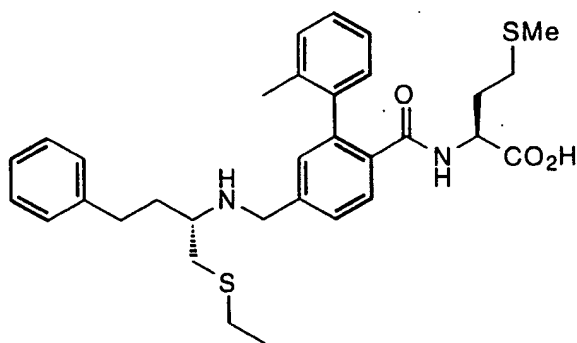
Example 986

N-[4-(N-2-Cyclohexylethyl-N-thiazol-5-ylmethylaminomethyl)-2-(2-methylphenyl)benzoyl]-methionine

9460

The desired compound was prepared according to the method of Example 157 ¹H nmr (300 MHz, DMSO d₆): δ 9.02, s, 1H; 8.09, d, 1H; 7.76, s, 1H; 7.48, d, 1H; 7.37, dd, 1H; 7.21, m, 2H; 7.15, m, 3H; 4.21, m, 1H; 3.83, s, 2H; 3.61, s, 2H; 2.42, t, 2H; 1.98 - 2.23, m, 6H; 1.96, s, 3H; 1.65 - 1.90, m, 2H; 1.55, m, 5H; 1.01 - 1.43, m, 6H; 0.80, m, 2H. MS (ESI(-)): 578 (M-H); (ESI(+)): 580. Calc'd for C₃₂H₄₁N₃O₃S₂: C 66.29, H 7.13, N 7.43: Found: C 65.82, H 7.03, N 7.34.

9465

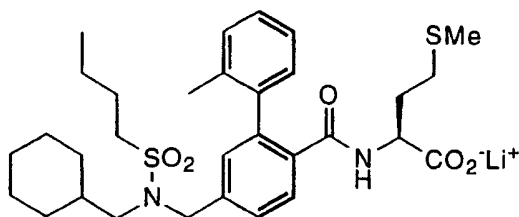
Example 995

N-[4-(1-ethylthio-4-phenylbut-2-oxymethyl)-2-(2-methylphenyl)benzoyl]-methionine

The desired compound was prepared according to the method of Example 158 ¹H (300MHz, CDCl₃, δ) 7.70 (1H, m), 7.38 (1H, dd, J=6&2Hz), 7.30-7.20 (6H, m), 7.20-7.05 (3H, m), 7.04 (1H, bs), 6.12 (1H, m), 6.00-5.40 (2H, m), 4.38 (1H, m), 4.01 (1H, m), 3.85 (1H, d, J=12Hz), 3.00-2.50 (5H, m), 2.37 (2H, m), 2.20-2.00 (6H, m), 1.98 (3H, s), 1.86 (2H, m), 1.57 (1H, m), 1.07 (3H, t, J=8Hz). m/e (ESI) 565 (MH⁺) Anal.calc. for C₃₂H₄₀N₂O₃S₂·0.50 H₂O C 66.98, H 7.20, N 4.88 Found C 67.02, H 7.24, N 4.80

9475

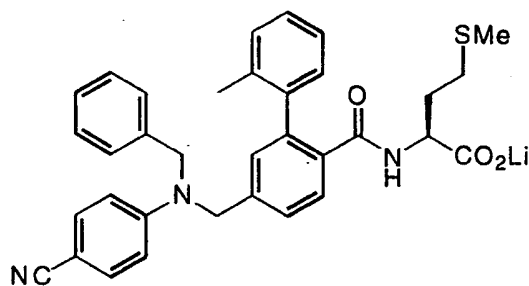
9480

**Example 996**

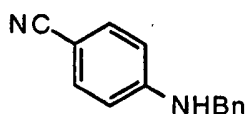
N-[4-(*N*-cyclohexylmethyl-*N*-butanesulfonylaminomethyl)-2-(2-methylphenyl)benzoyl]methionine

9485 The desired compound was prepared according to the method of Example 157. ¹H (300MHz, DMSO-d₆, δ) 7.54 (1H, m), 7.42 (1H, m), 7.30-7.10 (5H, m), 6.96 (1H, m), 4.40 (2H, m), 3.63 (1H, m), 3.08 (2H, m), 2.99 (2H, m), 2.17 (2H, m), 1.99 (2H, m), 1.90 (3H, s), 1.80-1.40 (10H, m), 1.37 (4H, m), 1.00 (2H, m), 1.87 (3H, t, J=8Hz), 1.73 (2H, m). m/e (ESI) 587 (MH⁻)

9490

**Example 997**

9495 *N*-[4-*N*-benzyl-*N*-(4-cyanophenyl)aminomethyl-2-(2-methylphenyl)benzoyl]methionine lithium salt

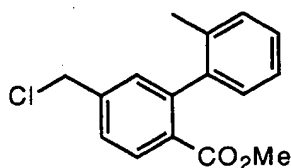
**Example 997A**

9500 A solution of 4-aminobenzonitrile (2.41 g, 20.0 mmol) and benzaldehyde (2.14 g, 20.0 mmol) in dichloroethane solvent (30 mL) was treated with Na(OAc)₃BH (6.69 g, 30.0 mmol) [CAUTION! - exothermic]. After 16 h the reaction mixture was carefully quenched by the addition of saturated aqueous NaHCO₃ (60 mL), and the resulting biphasic mixture was extracted with ethyl acetate (60 mL + 2 x 30 mL). The combined organic extracts were
9505 rinsed with brine (30 mL), dried over MgSO₄, and concentrated under reduced pressure to provide an amber oil. Flash column chromatography eluting with hexane and ethyl acetate

using an elution gradient of 90:10 to 80:20 afforded 3.56 g of 997A as a white solid (86% yield).

^1H NMR (CDCl_3): δ 4.37 (d, J = 5.4 Hz, 2 H), 2.58-4.66 (br, 1 H), 6.58 (d, J = 8.8 Hz, 2 H), 7.26-7.42 (comp, 7 H). LR

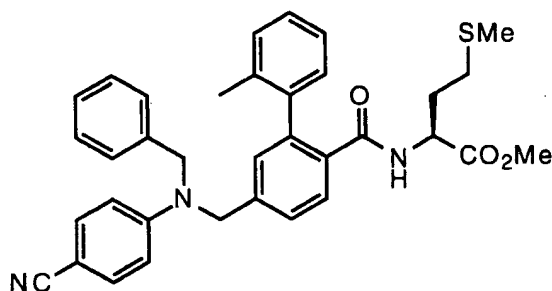
MS (CI^+): ($\text{M}+\text{H}$) $^+$ calc for $\text{C}_{14}\text{H}_{13}\text{N}_2$: 209; found: 209.



Example 997B

A solution of 1178C (2.50 g, 9.75 mmol) and lithium chloride (0.537 g, 12.7 mmol) in dimethyl formamide solvent (10 mL) was treated dropwise with a solution of thionyl chloride (1.78 g, 14.6 mmol) in dimethyl formamide solvent (5 mL). After 15 h the reaction mixture was poured into water (125 mL), and the resulting solution was extracted with diethyl ether (3 x 25 mL). The combined organic extracts were rinsed sequentially with water (2 x 20 mL), saturated aqueous sodium bicarbonate (3 x 20 mL), and then brine (20 mL). The organic portion was dried over MgSO_4 and concentrated under reduced pressure to provide a colorless oil. Flash column chromatography eluting with hexane and ethyl acetate using an elution gradient of 96:4 to 94:6 afforded 2.63 g of 997B as a colorless oil (98% yield).

^1H NMR (CDCl_3): δ 2.06 (s, 3 H), 3.61 (s, 3 H), 4.62 (s, 2 H), 7.07 (d, J = 7.0 Hz, 1 H), 7.17-7.31 (comp, 4 H), 7.45 (dd, J = 1.5, 8.1 Hz, 1 H), 7.97 (d, J = 8.1 Hz, 1 H). LR MS (CI^+): ($\text{M}+\text{H}$) $^+$ calc for $\text{C}_{16}\text{H}_{15}\text{ClO}_2$: 274; found: 274; ($\text{M}+\text{NH}_4$) $^+$ calc for $\text{C}_{16}\text{H}_{18}\text{ClNO}_2$: 292; found: 292.



Example 997C

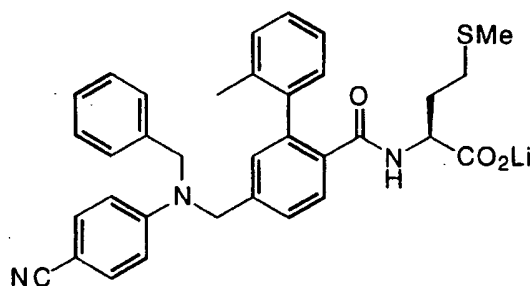
A heterogeneous mixture of 997A (0.466 g, 2.0 mmol), 4-chloromethyl-2-(2-methylphenyl)benzoic acid, methyl ester, 997B (0.550 g, 2.00 mmol), K_2CO_3 (0.553 g, 4.00 mmol), and tetrabutylammonium iodide (0.0754 g, 0.200 mmol) in acetonitrile solvent (5 mL) was heated to 70 $^\circ\text{C}$. After 16 h the reaction mixture was returned to room

temperature, diluted with dimethylformamide (DMF) solvent (5 mL) and treated with solid LiOH (0.514 g, 12.0 mmol), and then heated to 90 °C for 10 h. The reaction mixture was returned to room temperature and diluted with additional DMF (10 mL). Triethylamine hydrochloride (1.40 g, 10.0 mmol) was added, followed by methionine methyl ester hydrochloride (0.807 g, 4.00 mmol), 3-hydroxy-1,2,3-benzotriazin-4(3H)-one (HOGBT) (1.66 g, 10.0 mmol), and 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide (EDC) (1.96 g, 10.0 mmol). The mixture was heated to 60 °C for 18 h, cooled to room temperature, diluted with ethyl acetate (80 mL), and extracted with 2:1:1 H₂O: saturated aqueous NaHCO₃: brine (50 mL + 2 x 20 mL), followed by brine (10 mL). The organic layer was dried over MgSO₄, filtered through silica gel with 1:1 hexane: ethyl acetate rinses, and concentrated under reduced pressure to yield an amber oil. Radial chromatography eluting with hexane and ethyl acetate using an elution gradient of 80:20 to 50:50 afforded 0.0365 g of 997C as a colorless oil (3.2% yield).

¹H NMR (d₆-DMSO): δ 1.52-1.65 (m, 1 H), 1.79-1.91 (m, 1 H), 1.98-2.12 (comp, 8 H), 3.66 (s, 3 H), 4.56-4.67 (m, 1 H), 4.72 (s, 2 H), 4.75 (s, 2 H), 5.81-5.90 (br, 1 H), 6.69 (d, J = 8.9 Hz, 2 H), 7.00 (d, J = 1.7 Hz, 1 H), 7.15-7.88 (comp, 10 H), 7.42 (d, J = 8.9 Hz, 2 H), 7.93 (dd, J = 8.1, 13.2 Hz, 1 H). LR

MS (ESI⁺): (M+H)⁺ calc for C₃₅H₃₆N₃O₃S: 578; found: 578. LR

MS (ESI⁻): (M-H)⁻ calc for C₃₅H₃₄N₃O₃S: 576; found: 576.



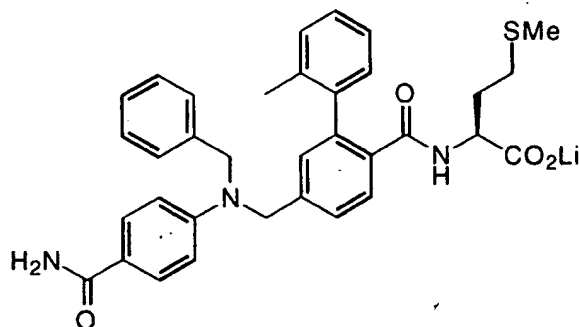
Example 997D

N-[4-N-benzyl-N-(4-cyanophenyl)aminomethyl]-2-(2-methylphenyl)benzoyl]methionine,
lithium salt

A solution of 997C (0.0375 g, 0.0649 mmol) in methanol solvent (0.3 mL) was treated with LiOH (0.078 mL of a 1 M aqueous solution, 0.078 mmol) to afford a cloudy, white mixture which gradually became clear and colorless. After 8 h the reaction mixture was diluted with H₂O (2 mL) and extracted with diethyl ether (2 x 1 mL). The aqueous phase was lyophilized to provide 0.0332 g of 997D as a white solid (90% yield).

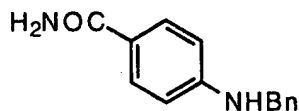
9565 ^1H NMR (d_6 -DMSO): δ 1.48-1.76 (comp, 2 H), 1.88-2.08 (comp, 8 H), 3.59-3.72 (br, 1 H), 4.83 (s, 2 H), 4.89 (s, 2 H), 6.76 (d, $J = 9.1$ Hz, 2 H), 6.90-6.96 (m, 1 H), 7.00 (s, 1 H), 7.07-7.37 (comp, 10 H), 7.47-7.53 (comp, 3 H). HR MS (FAB): $(\text{M}+\text{H})^+$ calc for $\text{C}_{34}\text{H}_{34}\text{N}_3\text{O}_3\text{S}$: 564.2321; found: 564.2325 (0.8 ppm error).

9570

Example 998

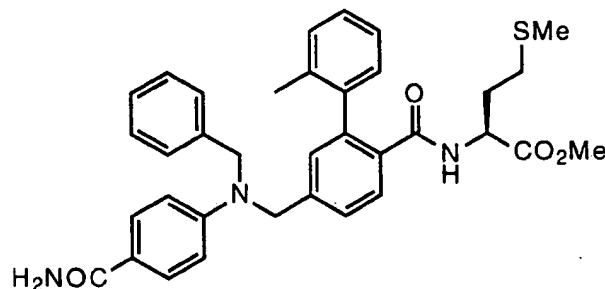
N-[4-N-benzyl-N-(4-carboxamidophenyl)aminomethyl-2-(2-methylphenyl)benzoyl]methionine, lithium salt

9575

Example 998A

Compound 998A was prepared in the same fashion as 997A (69% yield).

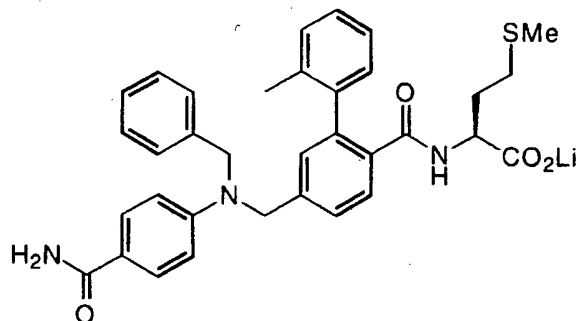
9580 ^1H NMR (d_6 -DMSO): δ 4.32 (d, $J = 5.9$ Hz, 2 H), 6.55 (d, $J = 8.6$ Hz, 2 H), 6.78-6.92 (br comp, 2 H), 7.20-7.26 (m, 1 H), 7.28-7.38 (comp, 4 H), 7.49-7.59 (br, 1 H), 7.60 (d, $J = 8.6$ Hz, 2 H). LR MS (CI $^+$): $(\text{M}+\text{H})^+$ calc for $\text{C}_{14}\text{H}_{15}\text{N}_2$: 227; found: 227.

Example 998B

Compound 998B was prepared in the same fashion as 997C (5.7% yield).

9585 ^1H NMR (d_6 -DMSO): δ 1.70-1.85 (comp, 2 H), 1.96 (s, 3 H), 1.97-2.24 (comp, 5 H), 3.58 (s, 3 H), 4.23-4.33 (br, 1 H), 4.80 (s, 2 H), 4.85 (s, 2 H), 6.68 (d, $J = 9.2$ Hz, 2

H), 6.86-6.94 (br, 1 H), 7.04-7.36 (comp, 14 H), 7.48 (d, $J = 8.2$ Hz, 1 H), 7.50-7.60 (br, 1 H), 7.63 (d, $J = 8.8$ Hz, 2 H), 8.30 (d, $J = 7.8$ Hz, 1 H): LR MS (ESI⁺): (M+H)⁺ calc for C₃₅H₃₈N₃O₄S: 596; found: 596. LR MS (ESI⁻): (M-H)⁻ calc for C₃₅H₃₆N₃O₄S: 594; found: 594.



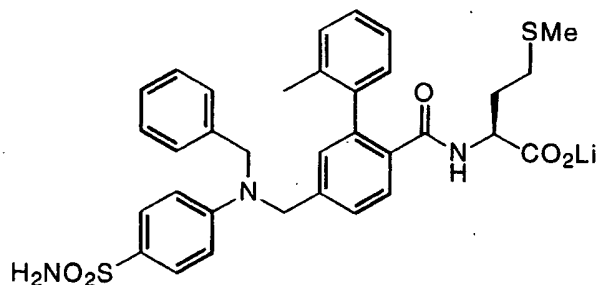
Example 998C

N-[4-N-benzyl-N-(4-carboxamidophenyl)aminomethyl-2-(2-methylphenyl)benzoyl]methionine, lithium salt

Compound 998C was prepared in the same fashion as 997D (100% yield).

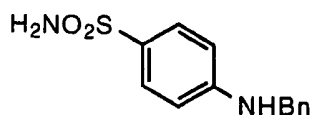
¹H NMR (d₆-DMSO): δ 1.47-1.61 (m, 1 H), 1.62-1.73 (m, 1 H), 1.87-2.08 (comp, 8 H), 3.59-3.70 (m, 1 H), 4.78 (s, 2 H), 6.67 (d, $J = 8.9$ Hz, 2 H), 6.86-6.94 (br comp, 2 H), 7.01 (s, 1 H), 7.05-7.35 (comp, 8 H), 7.50 (d, $J = 7.8$ Hz, 1 H), 7.54-7.61 (m, 1 H), 7.62 (d, $J = 8.9$ Hz, 1 H). HR

MS (FAB): (M+Li)⁺ calc for C₃₄H₃₅LiN₃O₄S: 588.2508; found: 588.2502 (-1.0 ppm error).



Example 999

N-[4-N-benzyl-N-(4-sulfonamidophenyl)aminomethyl-2-(2-methylphenyl)benzoyl]methionine, lithium salt

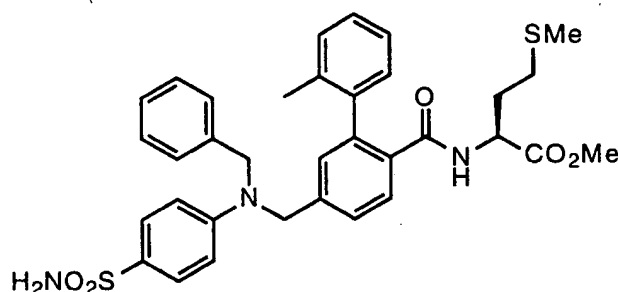


Example 999A

Compound 999A was prepared in the same fashion as 997A (51% yield).

9615 ^1H NMR (d_6 -DMSO): δ 4.34 (d, $J = 6.3$ Hz, 2 H), 6.63 (d, $J = 8.8$ Hz, 2 H), 6.90-6.94 (br, 2 H), 7.00-7.06 (m, 1 H), 7.20-7.26 (m, 1 H), 7.32-7.34 (comp, 4 H), 7.48 (d, $J = 8.8$ Hz, 2 H). LR

MS (CI $^+$): (M+H) $^+$ calc for $\text{C}_{13}\text{H}_{15}\text{N}_2\text{O}_2\text{S}$: 263; found: 263.



9620

Example 999B

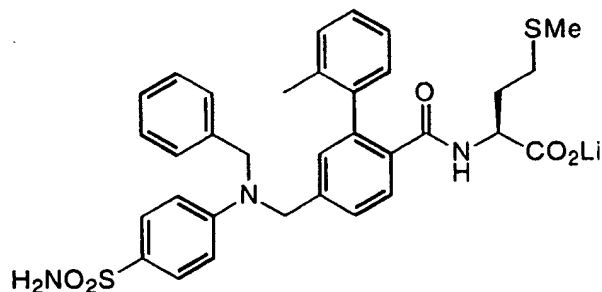
Compound 999B was prepared in the same fashion as 997C (1.3% yield).

9625 ^1H NMR (CDCl_3): δ 1.51-1.63 (m, 1 H), 1.78-1.91 (m, 1 H), 1.95-2.16 (comp, 8 H), 3.63 (app d, $J = 4.0$ Hz, 3 H), 4.14-4.20 (m, 2 H), 4.37 (d, $J = 5.1$ Hz, 2 H), 4.52-4.83 (comp, 3 H), 5.83-5.91 (m, 1 H), 6.59 (dd, $J = 2.6, 8.8$ Hz, 2 H), 7.07 (d, $J = 8.1$ Hz, 1 H), 7.24-7.40 (comp, 9 H), 7.61 (app t, $J = 7.4$ Hz, 2 H), 7.85 (dd, $J = 7.8, 18.0$ Hz, 1 H). LR

MS (ESI $^+$): (M+H) $^+$ calc for $\text{C}_{34}\text{H}_{38}\text{N}_3\text{O}_5\text{S}$: 632; found: 632. LR

MS (ESI $^-$): (M) $^-$ calc for $\text{C}_{34}\text{H}_{37}\text{N}_3\text{O}_5\text{S}$: 631; found: 631.

9630

Example 999C

N-[4-N-benzyl-N-(4-sulfonamidophenyl)aminomethyl]-2-(2-methylphenyl)benzoyl]methionine, lithium salt

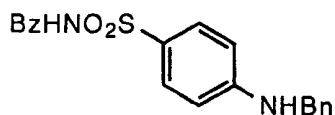
9635 Compound 999C was prepared in the same fashion as 997D (90% yield).

^1H NMR (d_6 -DMSO): δ 1.46-1.82 (comp, 2 H), 1.86-2.16 (comp, 8 H), 3.59-3.73 (m, 1 H), 3.99 (s, 2 H), 4.31 (app d, $J = 5.9$ Hz, 2 H), 6.55 (d, $J = 8.0$ Hz, 2 H), 6.74-7.37 (comp, 14 H), 7.72-7.80 (br, 1 H). HR

MS (FTMS): (M+H)⁺ calc for C₃₃H₃₆N₃O₃S₂: 618.2087; found: 618.2091 (-0.7 ppm error).

Example 1000

N-[4-N-benzyl-N-(4-N-benzoylsulfonamidophenyl)aminomethyl-2-(2-methylphenyl)benzoyl]methionine, lithium salt

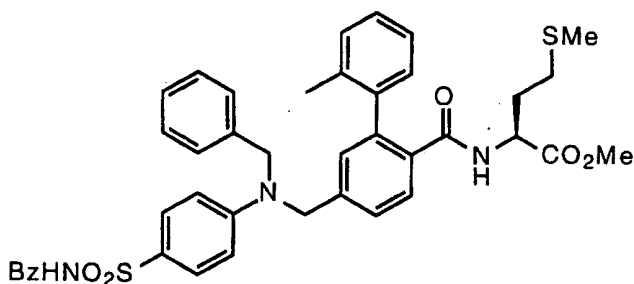


Example 1000A

Compound 1000A was prepared in the same fashion as 997A (81% yield).

¹H NMR (CDCl₃): δ 4.39 (d, J = 4.7 Hz, 2 H), 4.67-4.73 (br, 1 H), 6.62-6.67 (m, 2 H), 7.29-7.42 (comp, 5 H), 7.43-7.47 (comp, 2 H), 7.53-7.59 (m, 1 H), 7.74-7.79 (m, 2 H), 7.92-7.95 (m, 2 H), 8.46-8.80 (br, 1 H). LR

MS (CI⁺): (M+H)⁺ calc for C₂₀H₁₉N₂O₂S: 367; found: 367.



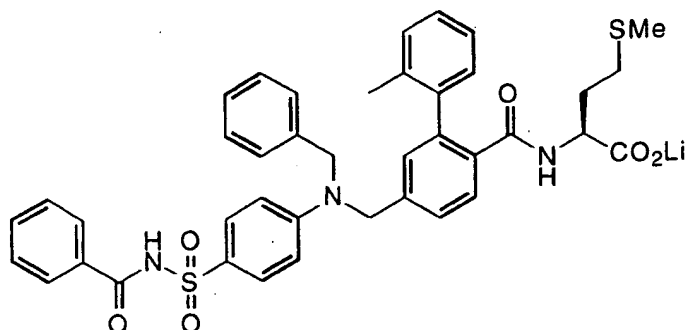
Example 1000B

Compound 1000B was prepared in the same fashion as 997C (5.6% yield).

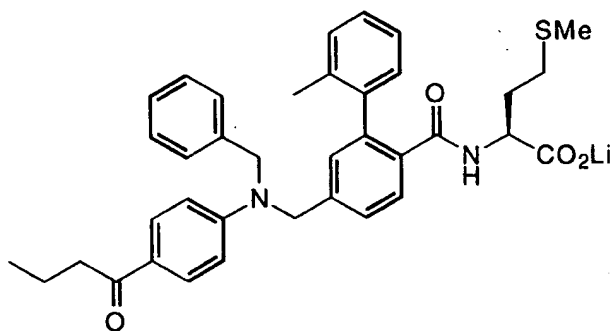
¹H NMR (CDCl₃): δ 1.52-1.66 (m, 1 H), 1.79-1.91 (m, 1 H), 1.99-2.10 (comp, 8 H), 3.65 (s, 3 H), 4.56-4.66 (m, 1 H), 4.72 (s, 2 H), 4.75 (s, 2 H), 5.86-5.93 (br, 1 H), 6.60-6.78 (comp, 2 H), 7.12-7.37 (comp, 9 H), 7.37-7.45 (comp, 3 H), 7.50-7.57 (m, 1 H), 7.87 (d, J = 7.8 Hz, 2 H), 7.86-7.94 (comp, 5 H), 8.02 (s, 1 H), 9.38 (s, 1 H), 10.70-10.86 (br, 1 H). LR

MS (ESI⁺): (M+H)⁺ calc for C₄₁H₄₂N₃O₆S: 736; found: 736. LR

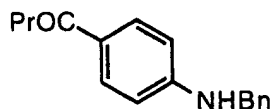
MS (ESI⁻): (M-H)⁻ calc for C₄₁H₄₀N₃O₆S: 734 found: 734.

Example 1000CN-[4-N-benzyl-N-(4-N-benzoylsulfonamidophenyl)aminomethyl-2-(2-methylphenyl)benzoyl]methionine, lithium salt

- 9670 Compound 1000C was prepared in the same fashion as 997D (77% yield).
¹H NMR (d₆-DMSO): δ 1.48-1.76 (comp, 2 H), 1.89-2.06 (comp, 8 H), 3.67-3.77 (br, 1 H), 4.29 (d, J = 5.9 Hz, 1 H), 4.74 (s, 2 H), 4.79 (s, 2 H), 6.49 (d, J = 8.9 Hz, 1 H), 6.60-6.66 (m, 2 H), 6.95-7.35 (comp, 15 H), 7.47-7.58 (comp, 2 H), 7.86 (d, J = 7.2 Hz, 2 H). LR
 9675 MS (ESI⁻): (M-H)⁻ calc for C₄₀H₃₈N₃O₆S₂: 720; found: 720.

Example 1001N-[4-N-benzyl-N-(4-propionylphenyl)aminomethyl-2-(2-methylphenyl)benzoyl]methionine, lithium salt

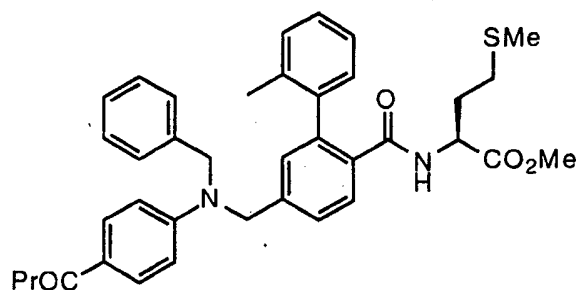
9680

Example 1001A

- 9685 Compound 1001A was prepared in the same fashion as 997A (89% yield).
¹H NMR (CDCl₃): δ 0.97 (t, J = 7.4 Hz, 3 H), 1.73 (tq, J = 7.3, 7.4 Hz, 2 H), 2.82 (t, J = 7.3 Hz, 2 H), 4.39 (d, J = 4.0 Hz, 2 H), 4.56-4.63 (br, 1 H), 6.59 (d, J = 9.0 Hz, 2 H), 7.25-7.35 (comp, 5 H), 7.82 (d, J = 9.0 Hz, 2 H). LR

MS (CI⁺): (M+H)⁺ calc for C₁₇H₂₀NO: 254; found: 254.

9690



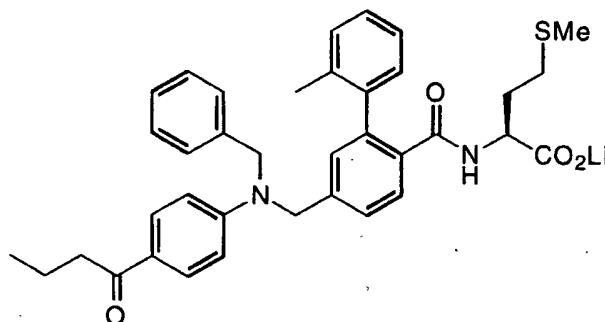
Example 1001B

Compound 1001B was prepared in the same fashion as 997C (49% yield).

¹H NMR (CDCl₃): δ 0.97 (t, J = 7.5 Hz, 3 H), 1.52-1.66 (m, 1 H), 1.73 (app q, J = 7.5 Hz, 2 H), 1.78-1.91 (m, 1 H), 1.99-2.13 (comp, 8 H), 2.82 (t, J = 7.5 Hz, 2 H), 3.66 (s, 3 H), 4.53-4.67 (m, 1 H), 4.73 (s, 2 H), 4.76 (s, 2 H), 5.84-5.90 (m, 1 H), 6.71 (d, J = 8.9 Hz, 2 H), 7.04 (d, J = 1.7 Hz, 1 H), 7.14-7.37 (comp, 10 H), 7.82 (d, J = 8.9 Hz, 2 H), 7.92 (dd, J = 8.1, 13.2 Hz, 1 H). LR

MS (ESI⁺): (M+H)⁺ calc for C₃₈H₄₃N₂O₄S: 623; found: 623. LR

9700 MS (ESI⁻): (M-H)⁻ calc for C₂₈H₄₁N₂O₄S: 621; found: 621.



Example 1001C

N-[4-N-benzyl-N-(4-propionylphenyl)aminomethyl-2-(2-methylphenyl)benzoyl]methionine, lithium salt

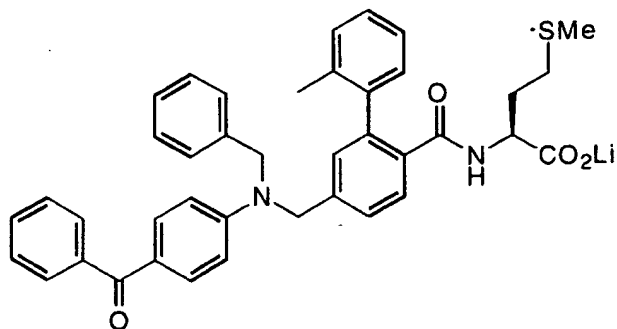
9705

Compound 1001C was prepared in the same fashion as 997D (98% yield).

¹H NMR (d₆-DMSO): δ 0.88 (t, J = 7.3 Hz, 3 H), 1.50-1.63 (comp, 3 H), 1.63-1.78 (m, 1 H), 1.79-2.11 (comp, 8 H), 2.78 (t, J = 7.3 Hz, 2 H), 3.72-3.81 (br, 1 H), 4.82 (s, 2 H), 4.87 (s, 2 H), 6.74 (d, J = 9.2 Hz, 2 H), 6.94-7.02 (br, 1 H), 7.02 (s, 1 H), 7.09-7.36 (comp, 10 H), 7.52 (d, J = 7.8 Hz, 1 H), 7.73 (d, J = 9.2 Hz, 2 H). HR

9710

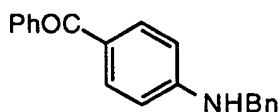
MS (FAB): (M+2Li-H)⁺ calc for C₃₇H₃₉Li₂N₂O₄S: 621.2951; found: 621.2966 (2.4 ppm error).



9715

Example 1002

N-[4-N-benzyl-N-(4-benzoylphenyl)aminomethyl-2-(2-methylphenyl)benzoyl]methionine,
lithium salt



9720

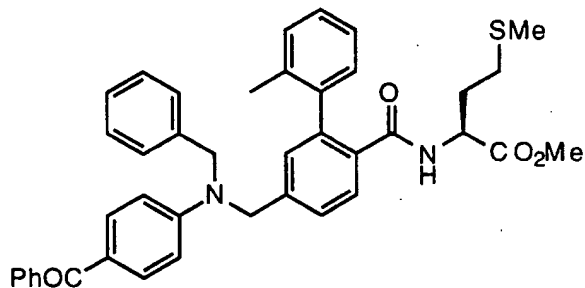
Example 1002A

Compound 1002A was prepared in the same fashion as 997A (63% yield).

^1H NMR (d_6 -DMSO): δ 3.37 (s, 1 H), 4.38 (d, J = 6.2 Hz, 2 H), 6.68 (d, J = 8.8 Hz, 2 H), 7.22-7.28 (m, 1 H), 7.31-7.38 (comp, 4 H), 7.46-7.62 (comp, 7 H). LR

9725 MS (ESI $^{+}$): (M+H) $^{+}$ calc for $\text{C}_{20}\text{H}_{18}\text{NO}$: 288; found: 288. LR

MS (ESI $^{-}$): (M-H) $^{-}$ calc for $\text{C}_{20}\text{H}_{16}\text{NO}$: 286; found: 286.

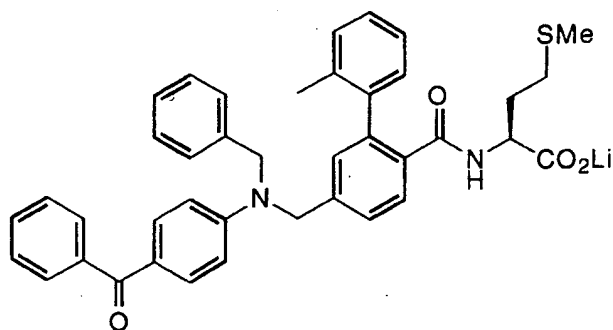
Example 1002B

9730 Compound 1002B was prepared in the same fashion as 997C (30% yield).

^1H NMR (CDCl_3): δ 1.52-1.68 (m, 1 H), 1.79-1.93 (m, 1 H), 1.98-2.16 (comp, 8 H), 3.67 (s, 3 H), 4.56-4.70 (m, 1 H), 4.76 (s, 2 H), 4.78 (s, 2 H), 5.85-5.92 (m, 1 H), 6.74 (d, J = 9.2 Hz, 2 H), 7.05 (s, 1 H), 7.14-7.38 (comp, 10 H), 7.40-7.48 (comp, 2 H), 7.69-7.78 (comp, 4 H), 7.94 (dd, J = 8.1, 13.3 Hz, 1 H). LR

9735 MS (ESI $^{+}$): (M+H) $^{+}$ calc for $\text{C}_{41}\text{H}_{41}\text{N}_2\text{O}_4\text{S}$: 657; found: 657. LR

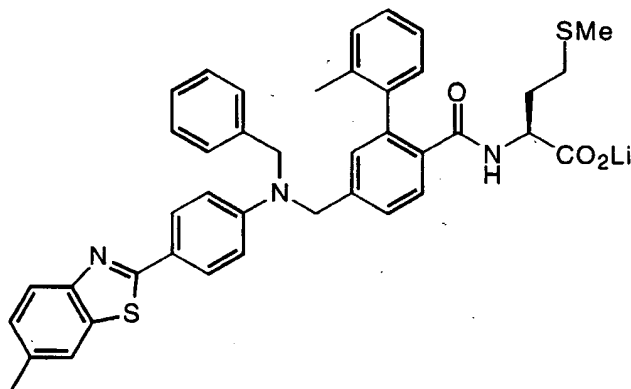
MS (ESI $^{-}$): (M-H) $^{-}$ calc for $\text{C}_{41}\text{H}_{39}\text{N}_2\text{O}_4\text{S}$: 655; found: 655.

Example 1002C

9740 N-[4-N-benzyl-N-(4-benzoylphenyl)aminomethyl-2-(2-methylphenyl)benzoyl]methionine,
lithium salt

Compound 1002C was prepared in the same fashion as 997D (86% yield).

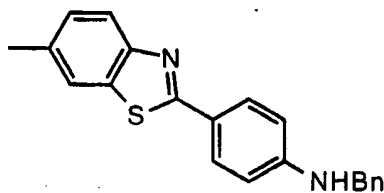
¹H NMR (d₆-DMSO): δ 1.49-1.63 (m, 1 H), 1.63-1.77 (m, 1 H), 1.78-2.10 (comp, 8 H), 3.68-3.76 (br, 1 H), 4.84 (s, 2 H), 4.89 (s, 2 H), 6.81 (d, J = 9.1 Hz, 2 H), 6.96 (d, J = 5.4 Hz, 1 H), 7.03 (s, 1 H), 7.08-7.37 (comp, 11 H), 7.46-7.61 (comp, 7 H). HR MS (FAB): (M+Li)⁺ calc for C₄₀H₃₈LiN₂O₄S: 649.2712; found: 649.2723 (1.6 ppm error). .



9750

Example 1003

N-[4-N-benzyl-N-(4-(6-methylbenzthiazol-2-yl)phenyl)aminomethyl-2-(2-
methylphenyl)benzoyl]methionine, lithium salt



9755

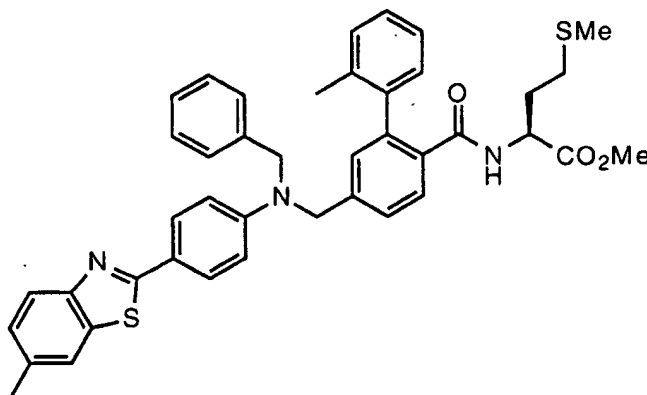
Example 1003A

Compound 1003A was prepared in the same fashion as 997A (38% yield).

^1H NMR (CDCl_3): δ 2.47 (s, 3 H), 4.41 (app s, 3 H), 6.65-6.70 (m, 2 H), 7.22-7.38 (comp, 6 H), 7.62 (s, 1 H), 7.83-7.91 (comp, 3 H). LR

9760 MS (ESI+): $(\text{M}+\text{H})^+$ calc for $\text{C}_{21}\text{H}_{19}\text{N}_2\text{S}$: 330; found: 330. LR

MS (ESI-): $(\text{M}-\text{H})^-$ calc for $\text{C}_{21}\text{H}_{17}\text{N}_2\text{S}$: 329; found: 329.



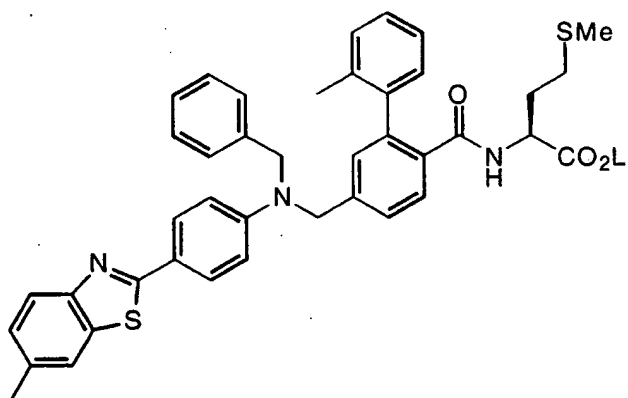
Example 1003B

9765 Compound 1003B was prepared in the same fashion as 997C (16% yield).

^1H NMR (CDCl_3): δ 1.52-1.72 (br m, 1 H), 1.80-1.92 (m, 1 H), 1.99-2.14 (comp, 8 H), 2.48 (s, 2 H), 3.66 (s, 3 H), 4.56-4.68 (m, 1 H), 4.74 (s, 2 H), 4.77 (s, 2 H), 5.84-5.90 (m, 1 H), 6.79 (d, $J = 8.8$ Hz, 2 H), 7.07 (s, 1 H), 7.24-7.38 (comp, 11 H), 7.62 (s, 2 H), 7.85-7.98 (comp, 4 H). LR

9770 MS (ESI+): $(\text{M}+\text{H})^+$ calc for $\text{C}_{42}\text{H}_{42}\text{N}_3\text{O}_3\text{S}_2$: 698; found: 698. LR

MS (ESI-): $(\text{M}-\text{H})^-$ calc for $\text{C}_{42}\text{H}_{40}\text{N}_3\text{O}_3\text{S}_2$: 700; found: 700.

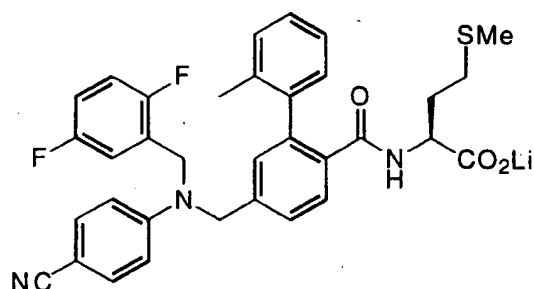


Example 1003C

9775 N-[4-N-benzyl-N-(4-(6-methylbenzothiazol-2-yl)phenyl)aminomethyl-2-(2-methylphenyl)benzoyl]methionine, lithium salt

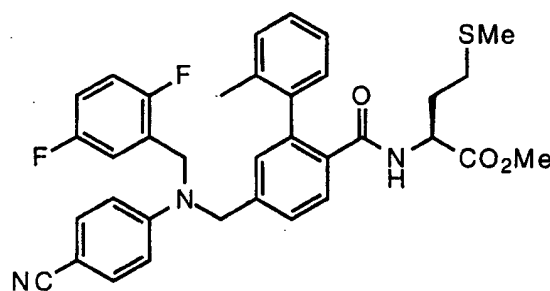
Compound 1003C was prepared in the same fashion as 997D (93% yield).

¹H NMR (d₆-DMSO): δ 1.48-1.62 (m, 1 H), 1.62-1.73 (m, 1 H), 1.80-2.11 (comp, 8 H), 2.41 (s, 3 H), 3.64-3.73 (br, 1 H), 4.82 (s, 2 H), 4.87 (s, 2 H), 6.83 (d, J = 8.8 Hz, 2 H), 6.95 (d, J = 5.8 Hz, 1 H), 7.04 (s, 1 H), 7.08-7.37 (comp, 11 H), 7.53 (d, J = 7.8 Hz, 1 H), 7.76-7.82 (comp, 4 H). HR MS (FAB): (M⁺)⁺ calc for C₄₁H₃₈N₃O₃S₂: 685.2433; found: 685.2421 (-1.8 ppm error).



Example 1004

N-[4-N-2,5-difluorobenzyl]-N-(4-cyanophenyl)aminomethyl-2-(2-methylphenyl)benzoyl]methionine, lithium salt



Example 1004A

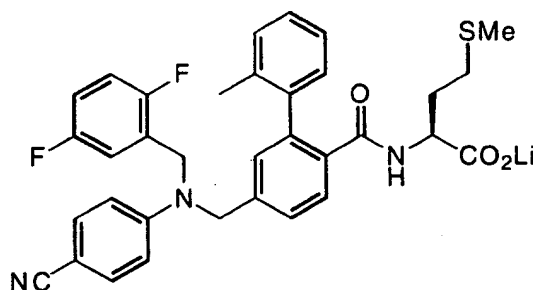
A heterogeneous mixture of 4-bromomethyl-2-(2-methylphenyl)benzoic acid, methyl ester (example 1178D) (0.638 g, 2.00 mmol), 4-aminobenzonitrile (0.241 g, 2.0 mmol), K₂CO₃ (1.11 g, 8.00 mmol), and tetrabutylammonium iodide (0.0754 g, 0.200 mmol) in acetonitrile solvent (5 mL) was heated to 70 °C for 18 h. Next, 2,5-difluorobenzyl bromide (0.507 g, 2.40 mmol) was added, and the reaction mixture was returned to 70 °C. After 16 h the reaction mixture was cooled to room temperature, diluted with DMF solvent (5 mL) and treated with solid LiOH (0.514 g, 12.0 mmol), and then heated to 90 °C for 14 h. The reaction mixture was cooled to room temperature and diluted with additional DMF (20 mL). Triethylamine hydrochloride (1.40 g, 10.0 mmol) was added, followed by methionine methyl ester hydrochloride (0.807 g, 4.00 mmol), 3-hydroxy-1,2,3-benzotriazin-4(3H)-one (HOBT) (1.66 g, 10.0 mmol), 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide (EDC) (1.96 g, 10.0 mmol), and finally, triethylamine (1.02 g, 10.0 mmol). The mixture was

heated to 60 °C for 8 h, cooled to room temperature, diluted with ethyl acetate (80 mL), and
 9805 extracted with 2:1:1 H₂O: saturated aqueous NaHCO₃: brine (50 mL + 2 x 20 mL),
 followed by brine (10 mL). The organic layer was dried over MgSO₄, filtered through silica
 gel with 1:1 hexane: ethyl acetate rinses, and concentrated under reduced pressure to yield
 an amber oil. Radial chromatography eluting with hexane and ethyl acetate using an elution
 gradient of 70:30 to 50:50 afforded 0.142 g of 1004A as a colorless oil (12% yield).

9810 ¹H NMR (CDCl₃): δ 1.53-1.66 (m, 1 H), 1.80-1.92 (m, 1 H), 1.98-2.12 (comp, 8 H),
 3.66 (s, 3 H), 4.56-4.67 (m, 1 H), 4.71 (s, 2 H), 4.75 (s, 2 H), 5.86-5.96 (m, 1 H), 6.69
 (d, J = 9.0 Hz, 2 H), 6.78-6.89 (comp, 2 H), 7.00 (s, 1 H), 7.04-7.37 (comp, 6 H), 7.44
 (d, J = 9.0 Hz, 2 H), 7.93 (dd, J = 8.1, 13.5 Hz, 1 H). LR

MS (ESI⁺): (M+H)⁺ calc for C₃₅H₃₄F₂N₃O₃S: 614; found: 614. LR

9815 MS (ESI⁻): (M-H)⁻ calc for C₃₅H₃₂F₂N₃O₃S: 612; found: 612.



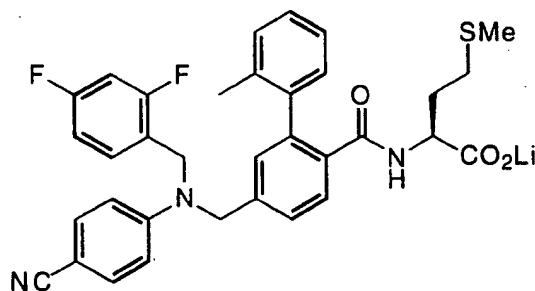
Example 1004B

N-[4-N-2,5-difluorobenzyl-N-(4-cyanophenyl)aminomethyl-2-(2-methylphenyl)
 9820 benzoyl]methionine, lithium salt

Compound 1004B was prepared in the same fashion as 997D (93% yield).

¹H NMR (d₆-DMSO): δ 1.50-1.80 (comp, 2 H), 1.90-2.12 (comp, 8 H), 3.64-3.81 (m, 1
 H), 4.84-5.00 (comp, 4 H), 6.75-6.88 (comp, 2 H), 6.89-7.08 (comp, 3 H), 7.11-7.40
 (comp, 6 H), 7.48-7.63 (comp, 3 H). HR

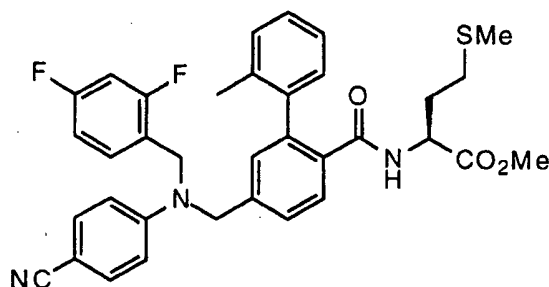
9825 MS (FAB): (M+H)⁺ calc for C₃₄H₃₂F₂N₃O₃S: 600.2132; found: 600.2139 (1.1 ppm
 error).



9830

Example 1005

N-[4-N-2,4-difluorobenzyl-N-(4-cyanophenyl)aminomethyl-2-(2-methylphenyl)benzoyl]methionine, lithium salt



9835

Example 1005A

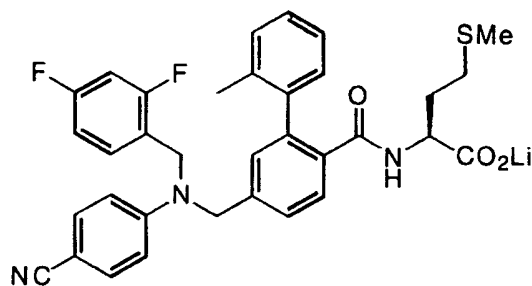
Compound 1005A was prepared starting from 4-bromomethyl-2-(2-methylphenyl)benzoic acid, methyl ester (example 1178D) in the same fashion as 1004A (14% yield).

¹H NMR (CDCl₃): δ 1.53-1.66 (m, 1 H), 1.80-1.92 (m, 1 H), 1.98-2.12 (comp, 8 H), 3.66 (s, 3 H), 4.56-4.67 (m, 1 H), 4.71 (s, 2 H), 4.75 (s, 2 H), 5.86-5.92 (m, 1 H), 6.69 (d, J = 9.0 Hz, 2 H), 6.79-6.89 (comp, 2 H), 7.00 (s, 1 H), 7.04-7.37 (comp, 6 H), 7.44 (d, J = 9.0 Hz, 2 H), 7.93 (dd, J = 8.1, 13.5 Hz, 1 H). LR

MS (ESI⁺): (M+H)⁺ calc for C₃₅H₃₄F₂N₃O₃S: 614; found: 614. LR

MS (ESI⁻): (M-H)⁻ calc for C₃₅H₃₂F₂N₃O₃S: 612; found: 612.

9845

Example 1005B

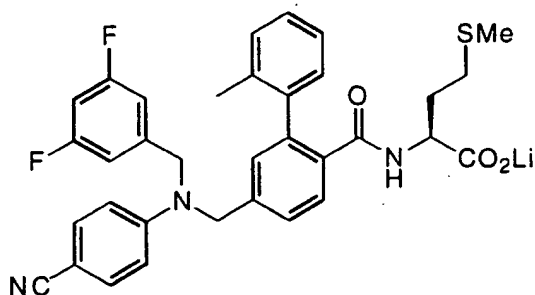
N-[4-N-2,4-difluorobenzyl-N-(4-cyanophenyl)aminomethyl-2-(2-methylphenyl)benzoyl]methionine, lithium salt

Compound 1005B was prepared in the same fashion as 997D (80% yield).

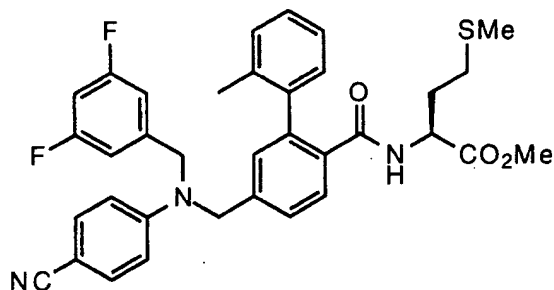
¹H NMR (d₆-DMSO): δ 1.48-1.62 (m, 1 H), 1.62-1.73 (m, 1 H), 1.89-2.07 (comp, 8 H), 3.62-3.72 (br, 1 H), 4.82-4.88 (comp, 4 H), 6.79 (d, J = 9.1 Hz, 2 H), 6.90-7.32 (comp, 10 H), 7.48-7.54 (comp, 3 H). HR

MS (FAB): (M+H)⁺ calc for C₃₄H₃₂F₂N₃O₃S: 600.2132; found: 600.2144 (2.0 ppm error).

9855

Example 1006

9860 N-[4-N-(3,5-difluorobenzyl)-N-(4-cyanophenyl)aminomethyl-2-(2-methylphenyl)benzoyl]methionine, lithium salt

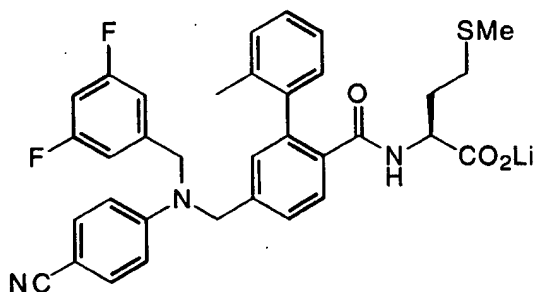
Example 1006A

9865 Compound 1006A was prepared starting from 4-bromomethyl-2-(2-methylphenyl)benzoic acid, methyl ester (example 1178D) in the same fashion as 1004A (28% yield).

¹H NMR (CDCl₃): δ 1.53-1.65 (m, 1 H), 1.80-1.91 (m, 1 H), 1.98-2.12 (comp, 8 H), 3.66 (s, 3 H), 4.56-4.66 (m, 1 H), 4.67 (s, 2 H), 4.76 (s, 2 H), 5.88 (d, J = 7.2 Hz, 1 H), 9870 6.64-6.76 (comp, 5 H), 7.00 (d, J = 1.3 Hz, 1 H), 7.13-7.36 (comp, 5 H), 7.44 (d, J = 8.8 Hz, 2 H), 7.94 (dd, J = 8.1, 13.2 Hz, 1 H). LR

MS (ESI⁺): (M+H)⁺ calc for C₃₅H₃₄F₂N₃O₃S: 614; found: 614. LR

MS (ESI⁻): (M-H)⁻ calc for C₃₅H₃₂F₂N₃O₃S: 612; found: 612.

Example 1006B

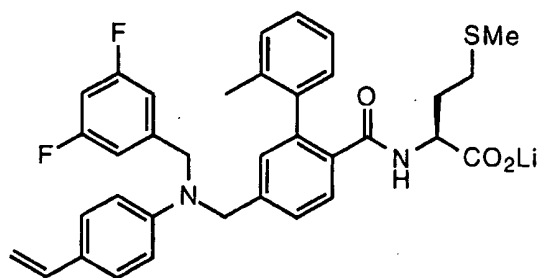
9875

N-[4-N-3,5-difluorobenzyl-N-(4-cyanophenyl)aminomethyl-2-(2-methylphenyl)benzoyl]methionine, lithium salt

Compound 1006B was prepared in the same fashion as 997D (82% yield).

9880 ¹H NMR (d₆-DMSO): δ 1.48-1.75 (comp, 2 H), 1.90-2.07 (comp, 8 H), 3.66-3.76 (br, 1 H), 4.86 (s, 2 H), 4.92 (s, 2 H), 6.76 (d, J = 8.8 Hz, 2 H), 6.92-7.00 (comp, 4 H), 7.07-7.24 (comp, 5 H), 7.30 (dd, J = 1.5, 8.12 Hz, 1 H), 7.50-7.55 (comp, 3 H). HR MS (FAB): (M+H)⁺ calc for C₃₄H₃₂F₂N₃O₃S: 600.2132; found: 600.2140 (1.2 ppm error).

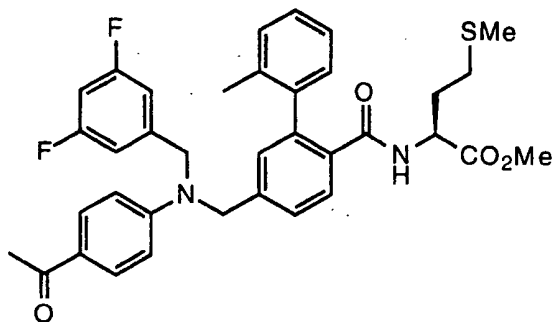
9885



Example 1007

N-[4-N-3,5-difluorobenzyl-N-(4-vinylphenyl)aminomethyl-2-(2-methylphenyl)benzoyl]methionine, lithium salt

9890

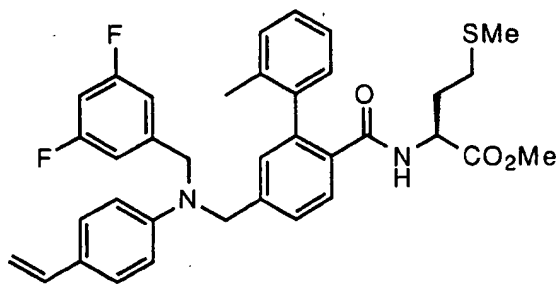


Example 1007A

9895 Compound 1007A was prepared starting from 4-bromomethyl-2-(2-methylphenyl)benzoic acid, methyl ester (example 1178D) in the same fashion as 1004A (11% yield).

9900 ¹H NMR (CDCl₃): δ 1.52-1.65 (m, 1 H), 1.80-1.91 (m, 1 H), 1.95-2.12 (comp, 8 H), 2.50 (s, 3 H), 3.67 (s, 3 H), 4.56-4.67 (m, 1 H), 4.70 (s, 2 H), 4.78 (s, 2 H), 5.89 (dd, J = 2.5, 7.7 Hz, 1 H), 6.65-6.77 (comp, 5 H), 7.04 (s, 1 H), 7.13-7.36 (comp, 5 H), 7.83 (d, J = 9.2 Hz, 2 H), 7.94 (dd, J = 8.1, 13.8 Hz, 1 H). LR MS (ESI⁺): (M+H)⁺ calc for C₃₆H₃₇F₂N₂O₄S: 631; found: 631. LR

MS (ESI⁻): (M-H)⁻ calc for C₃₆H₃₅F₂N₂O₄S: 629; found: 629.



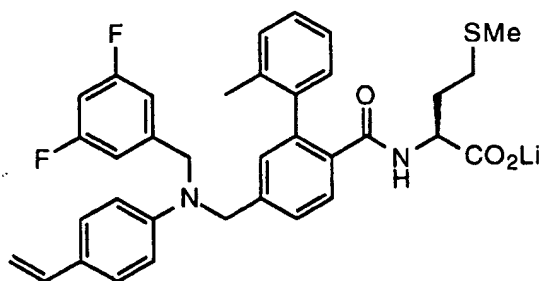
Example 1007B

A solution of 1007A (0.147 g, 0.233 mmol) in 1:1 tetrahydrofuran: methanol solvent (2 mL) was treated with NaBH₄ (0.0315 g, 0.815 mmol). After 1 h the mixture was quenched by the addition of H₂O (2 mL), followed by a few drops of 3 M HCl. The reaction mixture was then extracted with ethyl acetate (4 x 2 mL), and the combined organic extracts were rinsed with brine (1 mL), dried over MgSO₄, filtered through silica gel with ethyl acetate rinses, and concentrated under reduced pressure to afford an amber oil. Radial chromatography eluting with hexane and ethyl acetate using an elution gradient of 60:40 to 30:70 afforded 0.0097 g of 1007B as a colorless oil (6.8% yield).

¹H NMR (CDCl₃): δ 1.52-1.62 (comp, 2 H), 1.80-1.91 (m, 1 H), 1.99-2.14 (comp, 8 H), 3.66 (s, 3 H), 4.58-4.66 (comp, 3 H), 4.70 (s, 2 H), 5.04 (d, J = 11.1 Hz, 1 H), 5.53 (d, J = 17.6 Hz, 1 H), 5.84-5.90 (m, 1 H), 6.55-6.67 (comp, 3 H), 6.67-6.79 (comp, 2 H), 7.05 (s, 1 H), 7.23-7.34 (comp, 8 H), 7.92 (dd, J = 8.1, 13.6 Hz, 1 H). LR

MS (ESI⁺): (M+H)⁺ calc for C₃₆H₃₇F₂N₂O₃S: 615; found: 615. LR

MS (ESI⁻): (M-H)⁻ calc for C₃₆H₃₅F₂N₂O₃S: 613; found: 613.

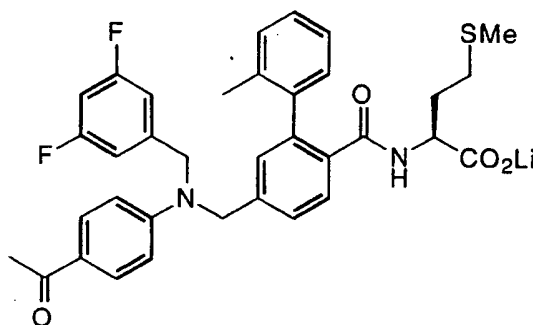


Example 1007C

N-[4-N-3,5-difluorobenzyl-N-(4-vinylphenyl)aminomethyl-2-(2-methylphenyl)benzoyl]methionine, lithium salt

Compound 1007C was prepared in the same fashion as 997D (72% yield). ¹H NMR (d₆-DMSO): δ 1.60-1.70 (br m, 1 H), 1.70-1.83 (br m, 1 H), 1.88-2.06 (br comp, 8 H), 3.58-3.68 (br, 1 H), 4.65-4.77 (br comp, 1 H), 4.75 (s, 2 H), 4.81 (s, 2 H),

4.96 (d, $J = 11.0$ Hz, 1 H), 5.51 (dd, $J = 1.2, 17.7$ Hz, 1 H), 6.54 (dd, $J = 11.0, 17.7$ Hz, 1 H), 6.65 (d, $J = 9.2$ Hz, 2 H), 6.89-7.00 (comp, 4 H), 7.01-7.22 (comp, 4 H), 7.23 (d, $J = 9.2$ Hz, 2 H), 7.30-7.33 (m, 1 H), 7.51 (d, $J = 7.9$ Hz, 1 H). LR MS (ESI⁻): (M-H)⁻ calc for C₃₅H₃₂F₂LiN₃O₃S: 599; found: 599.



9935

1008

N-[4-N-3,5-difluorobenzyl-N-(4-acetylphenyl)aminomethyl-2-(2-methylphenyl)benzoyl]methionine, lithium salt

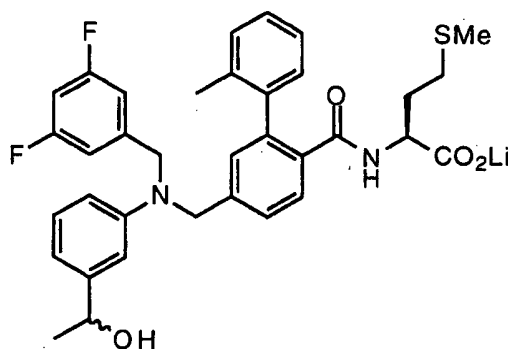
Compound 1008 was prepared in the same fashion as 997D (86% yield).

¹H NMR (d₆-DMSO): δ 1.46-1.61 (m, 1 H), 1.61-1.73 (m, 1 H), 1.86-2.08 (comp, 8 H), 2.38 (s, 3 H), 3.58-3.68 (br, 1 H), 4.85 (s, 2 H), 4.90 (s, 2 H), 6.73 (d, $J = 9.0$ Hz, 2 H), 6.90-7.00 (comp, 5 H), 7.05-7.20 (comp, 5 H), 7.30 (dd, $J = 1.7, 7.8$ Hz, 1 H), 7.52 (d, $J = 7.8$ Hz, 1 H), 7.74 (d, 9.0 Hz, 2 H). HR

9940

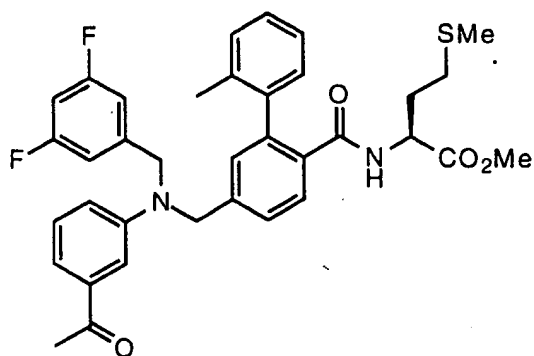
MS (FAB): (M+H)⁺ calc for C₃₅H₃₅F₂N₂O₄S: 617.2286; found: 617.2277 (-1.5 ppm error).

9945

Example 1009

N-[4-N-3,5-difluorobenzyl-N-(4-(1-hydroxyethyl)phenyl)aminomethyl-2-(2-methylphenyl)benzoyl]methionine, lithium salt

9950

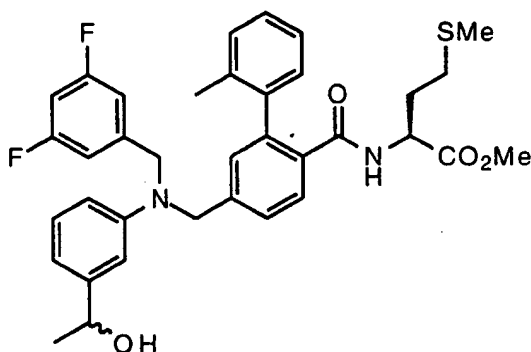
Example 1009A

Compound 1009A was prepared starting from 4-chloromethyl-2-(2-methylphenyl)benzoic acid, methyl ester (example 997B) in the same fashion as 1004A (17% yield).

^1H NMR (CDCl_3): δ 1.52-1.65 (m, 1 H), 1.79-1.91 (m, 1 H), 2.00-2.14 (comp, 8 H), 2.52 (s, 3 H), 2.67 (s, 3 H), 4.56-4.66 (m, 1 H), 4.66 (s, 2 H), 4.74 (s, 2 H), 5.85-5.91 (m, 1 H), 6.64-6.81 (comp, 3 H), 6.86 (d, $J = 8.1$ Hz, 1 H), 7.05 (s, 1 H), 7.14-7.35 (comp, 8 H), 7.92 (dd, $J = 8.1, 14.0$ Hz, 1 H). LR

MS (ESI $^+$): ($M+H$) $^+$ calc for $\text{C}_{36}\text{H}_{37}\text{F}_2\text{N}_2\text{O}_4\text{S}$: 631; found: 631. LR

MS (ESI $^-$): ($M-H$) $^-$ calc for $\text{C}_{36}\text{H}_{35}\text{F}_2\text{N}_2\text{O}_4\text{S}$: 629; found: 629.

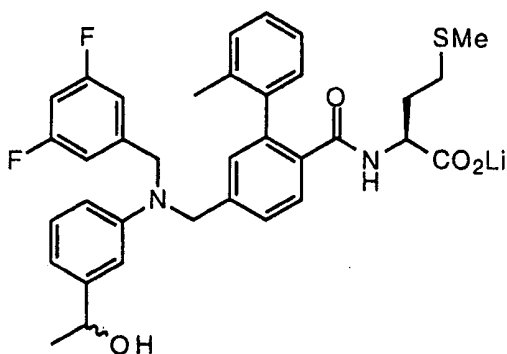
Example 1009B

Compound 1009B was prepared in the same fashion as 1007B (10% yield).

^1H NMR (CDCl_3): δ 1.41 (d, $J = 6.5$ Hz, 3 H), 1.52-1.65 (comp, 2 H), 1.77 (d, $J = 2.7$ Hz, 1 H), 1.79-1.91 (m, 1 H), 1.99-2.15 (comp, 8 H), 3.66 (s, 3 H), 4.56-4.65 (comp, 3 H), 4.69 (s, 2 H), 4.73-4.82 (m, 1 H), 5.85-5.91 (m, 1 H), 6.59 (dd, $J = 2.4, 8.2$ Hz, 1 H), 6.64-6.80 (comp, 5 H), 7.06 (d, $J = 1.3$ Hz, 1 H), 7.15-7.19 (m, 1 H), 7.21-7.36 (comp, 5 H), 7.92 (dd, $J = 8.1, 14.3$ Hz, 1 H). LR

MS (ESI $^+$): ($M+H$) $^+$ calc for $\text{C}_{36}\text{H}_{39}\text{F}_2\text{N}_2\text{O}_4\text{S}$: 633; found: 633. LR

MS (ESI $^-$): ($M-H$) $^-$ calc for $\text{C}_{36}\text{H}_{37}\text{F}_2\text{N}_2\text{O}_4\text{S}$: 631; found: 631.



9975

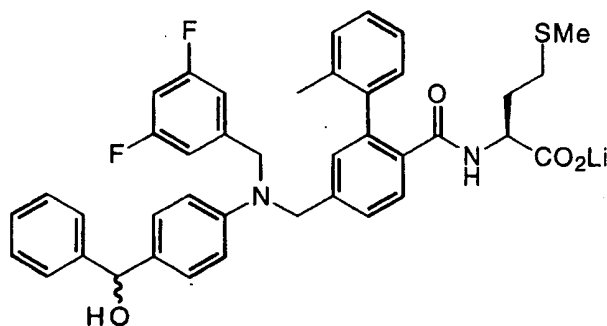
Example 1009C

N-[4-N-3,5-difluorobenzyl-N-(4-(1-hydroxyethyl)phenyl)aminomethyl]-2-(2-methylphenyl)benzoyl]methionine, lithium salt

Compound 1009C was prepared in the same fashion as 997D (76% yield).

9980 ^1H NMR (d_6 -DMSO): δ 1.18 (d, $J = 6.1$ Hz, 3 H), 1.47-1.60 (m, 1 H), 1.60-1.73 (m, 1 H), 1.88-2.09 (comp, 8 H), 3.59-3.68 (m, 1 H), 4.89-4.57 (m, 1 H), 4.71 (s, 2 H), 4.78 (s, 2 H), 4.99 (d, $J = 4.1$ Hz, 1 H), 6.50 (dd, $J = 2.3, 8.4$ Hz, 1 H), 6.61 (d, $J = 7.4$ Hz, 1 H), 6.70 (s, 1 H), 6.89-7.03 (comp, 4 H), 7.03-7.21 (dd, $J = 1.3, 7.8$ Hz, 1 H), 7.51 (d, $J = 9.8$ Hz, 1 H). HR

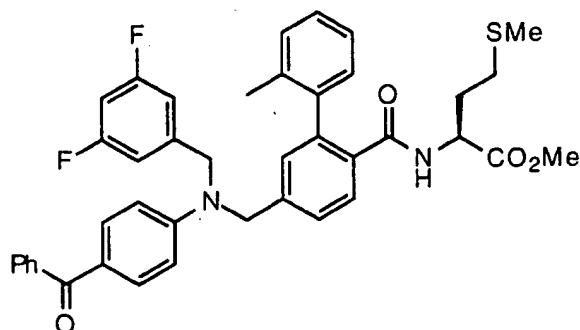
9985 MS (FAB): $(\text{M}+\text{H})^+$ calc for $\text{C}_{35}\text{H}_{36}\text{F}_2\text{N}_3\text{O}_4\text{S}$: 618.2364; found: 618.2366 (0.4 ppm error).



9990

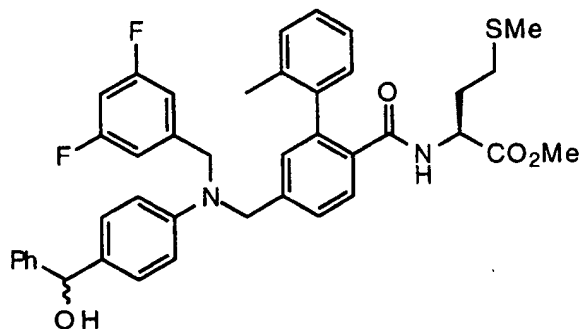
Example 1010

N-[4-N-3,5-difluorobenzyl-N-(4-(1-hydroxy-1-phenylmethyl)phenyl)aminomethyl]-2-(2-methylphenyl)benzoyl]methionine, lithium salt

**Example 1010A**

Compound 1010A was prepared starting from 4-chloromethyl-2-(2-methylphenyl)benzoic acid, methyl ester (example 997B) in the same fashion as 1004A (5.4% yield).

^1H NMR (CDCl_3): δ 1.53-1.66 (m, 1 H), 1.80-1.91 (m, 1 H), 2.00-2.13 (comp, 8 H), 3.66 (s, 3 H), 4.55-4.66 (m, 1 H), 4.71 (s, 2 H), 4.79 (s, 2 H), 5.86-5.92 (m, 1 H), 6.68-6.78 (comp, 5 H), 7.05 (d, $J = 1.6$ Hz, 1 H), 7.14-7.35 (comp, 6 H), 7.40-7.47 (comp, 2 H), 7.49-7.55 (m, 1 H), 7.70-7.77 (comp, 4 H), 7.94 (dd, $J = 8.2, 13.3$ Hz, 1 H). LR MS (ESI $^-$): (M-H) $^-$ calc for $\text{C}_{41}\text{H}_{37}\text{F}_2\text{N}_2\text{O}_4\text{S}$: 691; found: 691.

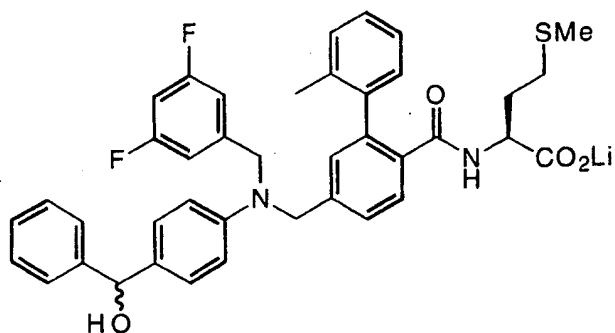
**Example 1010B**

Compound 1010B was prepared in the same fashion as 1007B (6.5% yield).

^1H NMR (CDCl_3): δ 1.52-1.64 (comp, 2 H), 1.78-1.91 (m, 1 H), 1.99-2.11 (comp, 8 H), 3.66 (s, 3 H), 4.55-4.65 (comp, 3 H), 4.68 (s, 2 H), 5.70 (d, $J = 2.9$ Hz, 1 H), 5.86 (t, $J = 6.4$ Hz, 1 H), 6.63 (d, $J = 8.5$ Hz, 2 H), 6.67-6.72 (m, 1 H), 6.75 (d, $J = 6.2$ Hz, 2 H), 7.04 (s, 1 H), 7.17 (d, $J = 8.5$ Hz, 2 H), 7.19-7.41 (comp, 10 H), 7.91 (dd, $J = 8.0, 21.3$ Hz, 1 H). LR

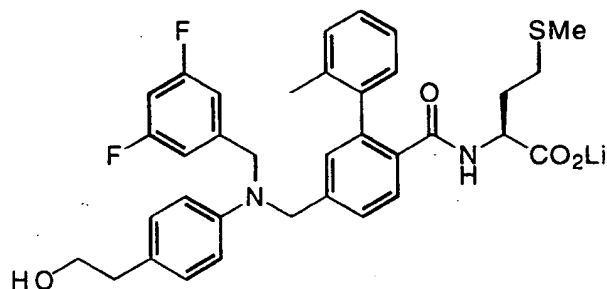
MS (ESI $^+$): (M-OH) $^+$ calc for $\text{C}_{41}\text{H}_{39}\text{F}_2\text{N}_2\text{O}_3\text{S}$: 677; found: 677. LR

MS (ESI $^-$): (M-H) $^-$ calc for $\text{C}_{41}\text{H}_{39}\text{F}_2\text{N}_2\text{O}_4\text{S}$: 693; found: 693.

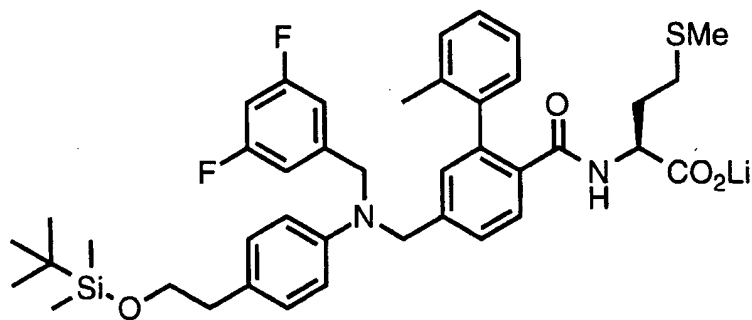
**Example 1010C**

N-[4-N-3,5-difluorobenzyl-N-(4-(1-hydroxy-1-phenylmethyl)phenyl)aminomethyl]-2-(2-methylphenyl)benzoyl]methionine, lithium salt

- 10020 Compound 1010C was prepared in the same fashion as 997D (100% yield).
¹H NMR (d₆-DMSO): δ 1.50-1.59 (br m, 1 H), 1.62-1.70 (br m, 1 H), 1.88-2.23 (br comp, 8 H), 4.68 (s, 2 H), 4.77 (s, 2 H), 6.66 (d, J = 8.5 Hz, 2 H), 6.92-6.95 (comp, 3 H), 7.02-7.07 (comp, 3 H), 7.11-7.26 (comp, 5 H), 7.27-7.32 (comp, 5 H), 7.49 (d, J = 8.0 Hz, 1 H). LR
- 10025 MS (ESI⁻): (M-H)⁻ calc for C₄₀H₃₇F₂LiN₂O₄S: 678; found: 678.

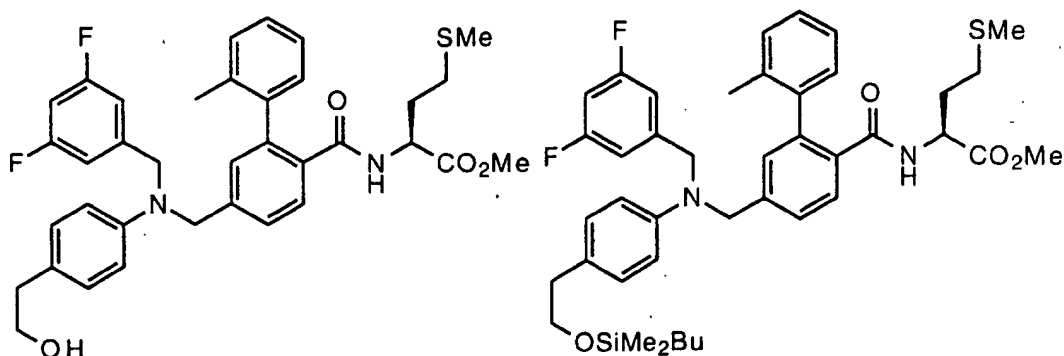
**Example 1011**

- 10030 N-[4-N-3,5-difluorobenzyl-N-(4-(2-hydroxyethyl)phenyl)aminomethyl]-2-(2-methylphenyl)benzoyl]methionine, lithium salt

**Example 1012**

10035

N-[4-N-3,5-difluorobenzyl]-N-(4-(2-hydroxyethyl)phenyl)aminomethyl-
2-(2-methylphenyl)benzoyl]methionine, lithium salt



Example 1011A and Example 1012A

10040

Compound 1012A was prepared starting from 4-chloromethyl-2-(2-methylphenyl)benzoic acid, methyl ester, 997B, in the same fashion as 1004A (4.1% yield). Compound 1011A was isolated from the crude reaction mixture as a side-product (15% yield).

10045

$^1\text{H NMR}$ (CDCl_3): δ 1.44-1.50 (br, 1 H), 1.52-1.65 (m, 1 H), 1.80-1.91 (m, 1 H), 1.99-2.12 (comp, 8 H), 2.76 (t, $J = 6.4$ Hz, 2 H), 3.66 (s, 3 H), 3.80 (br t, $J = 6.4$ Hz, 2 H), 4.58-4.68 (comp, 5 H), 5.84-5.90 (m, 1 H), 6.64 (d, $J = 8.5$ Hz, 2 H), 6.66-6.72 (m, 1 H), 6.77 (d, $J = 5.7$ Hz, 2 H), 7.04 (d, $J = 8.8$ Hz, 2 H), 7.07 (s, 1 H), 7.20-7.34 (comp, 5 H), 7.91 (dd, $J = 8.2, 13.6$ Hz, 1 H). LR

MS (ESI⁺): ($\text{M}+\text{H}$)⁺ calc for $\text{C}_{36}\text{H}_{39}\text{F}_2\text{N}_2\text{O}_4\text{S}$: 633; found: 633. LR

10050

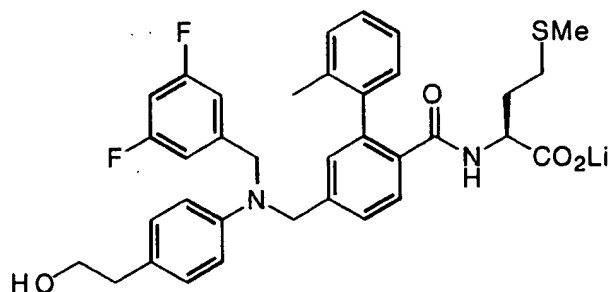
MS (ESI⁻): ($\text{M}-\text{H}$)⁻ calc for $\text{C}_{36}\text{H}_{37}\text{F}_2\text{N}_2\text{O}_4\text{S}$: 631; found: 631. 1012A:

$^1\text{H NMR}$ (CDCl_3): δ -0.04 (s, 6 H), 0.86 (s, 9 H), 1.52-1.64 (m, 1 H), 1.79-1.91 (m, 1 H), 1.99-2.12 (comp, 8 H), 2.71 (t, $J = 7.2$ Hz, 2 H), 3.65 (s, 3 H), 3.73 (t, $J = 7.2$ Hz, 2 H), 4.56 (s, 2 H), 4.60-4.70 (comp, 3 H), 5.83-5.89 (m, 1 H), 6.62 (d, $J = 8.4$ Hz, 2 H), 6.65-6.71 (m, 1 H), 6.76 (d, $J = 6.1$ Hz, 2 H), 7.01 (d, $J = 8.4$ Hz, 2 H), 7.06 (d, $J = 1.7$ Hz, 1 H), 7.20-7.34 (comp, 5 H), 7.90 (dd, $J = 8.1, 13.2$ Hz, 1 H). LR

10055

MS (ESI⁺): ($\text{M}+\text{H}$)⁺ calc for $\text{C}_{42}\text{H}_{53}\text{F}_2\text{N}_2\text{O}_4\text{SiS}$: 747; found: 747. LR

MS (ESI⁻): ($\text{M}-\text{H}$)⁻ calc for $\text{C}_{42}\text{H}_{51}\text{F}_2\text{N}_2\text{O}_4\text{SiS}$: 745; found: 745.



10060

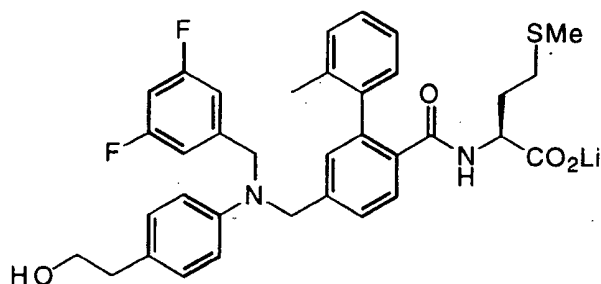
Example 1011BN-[4-N-3,5-difluorobenzyl-N-(4-(2-hydroxyethyl)phenyl)aminomethyl-
2-(2-methylphenyl)benzoyl]methionine, lithium salt

Compound 1011B was prepared in the same fashion as 997D (76% yield).

¹H NMR (d₆-DMSO): δ 1.48-1.74 (br comp, 2 H), 1.90-2.06 (br comp, 8 H), 2.56 (t, J = 7.2 Hz, 2 H), 3.48 (t, J = 7.2 Hz, 2 H), 3.64-3.76 (br, 1 H), 4.69 (s, 2 H), 4.75 (s, 2 H), 6.58 (d, J = 8.5 Hz, 2 H), 6.90-7.22 (br comp, 10 H), 7.30 (d, J = 7.8 Hz, 1 H), 7.50 (d, J = 8.1 Hz, 1 H). HR

MS (FAB): (M+H)⁺ calc for C₃₅H₃₆F₂LiN₂O₄S: 625.2524; found: 625.2542 (2.8 ppm error).

10070

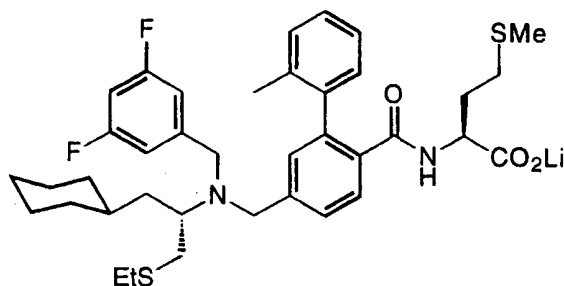
(258473) Example 1012BN-[4-N-3,5-difluorobenzyl-N-(4-(2-hydroxyethyl)phenyl)aminomethyl-
2-(2-methylphenyl)benzoyl]methionine, lithium salt

Compound 1012B was prepared in the same fashion as 997D (64% yield).

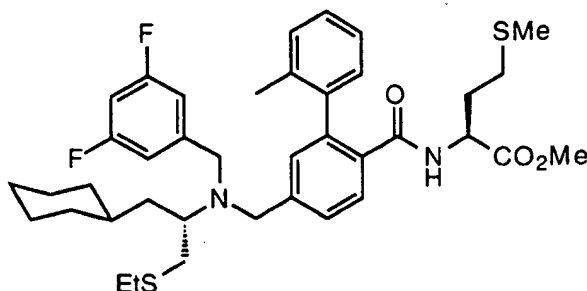
¹H NMR (d₆-DMSO): δ -0.12 (s, 6 H), 0.79 (s, 9 H), 1.48-1.74 (br comp, 2 H), 1.89-2.08 (br comp, 8 H), 2.56 (t, J = 6.9 Hz, 2 H), 3.65 (t, J = 6.9 Hz, 2 H), 4.69 (s, 2 H), 4.76 (s, 2 H), 6.58 (d, J = 8.9 Hz, 2 H), 6.88-7.22 (comp, 10 H), 7.30 (d, J = 7.7 Hz, 1 H), 7.49 (d, J = 7.7 Hz, 1 H). HR

MS (FAB): (M+H)⁺ calc for C₄₁H₅₀F₂LiN₂O₄Si: 739.3389; found: 739.3389 (0.1 ppm error).

10085

Example 1013

N-[4-N-3,5-difluorobenzyl-N-(1-ethylthio-3-cyclohexylprop-2-yl)aminomethyl-2-(2-methylphenyl)benzoyl] methionine.



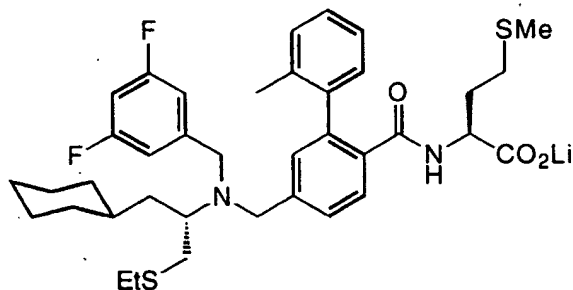
Example 1013A

Compound 1013A was prepared starting from 4-bromomethyl-2-(2-methylphenyl)benzoic acid, methyl ester (example 1178D) in the same fashion as 1004A (10% yield).

¹H NMR (CDCl₃): δ 0.70-0.93 (comp, 2 H), 1.06-1.71 (comp, 16 H), 1.30-1.92 (m, 1 H), 1.99-2.10 (comp, 7 H), 2.19 (s, 1 H), 2.39-2.48 (comp, 3 H), 2.77-2.89 (comp, 2 H), 3.58-3.71 (comp, 7 H), 4.56-4.70 (m, 1 H), 5.89 (d, J = 7.4 Hz, 1 H), 6.61-6.70 (m, 1 H), 6.94 (d, J = 8.1 Hz, 2 H), 7.15-7.22 (m, 1 H), 7.22-7.37 (comp, 9 H), 7.50 (d, J = 8.1 Hz, 1 H), 7.92 (dd, J = 8.1, 15.1 Hz, 1 H). LR

MS (ESI⁺): (M+H)⁺ calc for C₃₉H₅₁F₂N₂O₃S₂: 697; found: 697. LR

MS (ESI⁻): (M-H)⁻ calc for C₃₉H₄₉F₂N₂O₃S₂: 695; found: 695.



Example 1013B

N-[4-N-3,5-difluorobenzyl-N-(1-ethylthio-3-cyclohexylprop-2-yl)aminomethyl-2-(2-methylphenyl)benzoyl] methionine.

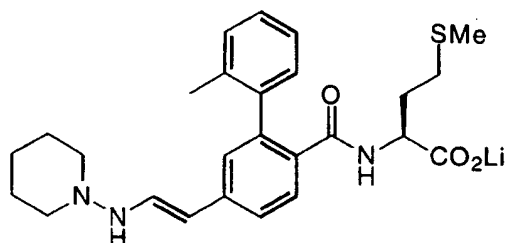
Compound 1013B was prepared in the same fashion as 997D (76% yield).

¹H NMR (d₆-DMSO): δ 0.59-0.74 (m, 1 H), 0.74-0.91 (m, 1 H), 0.97-1.18 (comp, 4 H), 1.21-1.33 (comp, 2 H), 1.36-1.75 (comp, 8 H), 1.76-1.87 (m, 1 H), 1.88-1.96 (comp, 2 H), 1.96-2.02 (comp, 2 H), 2.15-2.22 (br, 1 H), 2.34-2.45 (comp, 3 H), 2.60-2.70 (br, 1 H), 2.94 (dd, J = 5.9, 12.9 Hz, 1 H), 3.32-3.45 (comp, 4 H), 3.57-3.74 (br comp, 5 H),

6.93 (d, $J = 6.3$ Hz, 1 H), 7.03-7.25 (comp, 7 H), 7.38 (d, $J = 7.3$ Hz, 1 H), 7.50 (d, $J = 7.7$ Hz, 1 H). HR

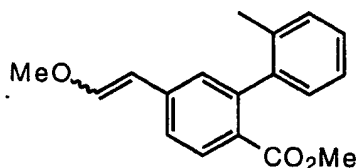
MS (FAB): $(M+H)^+$ calc for $C_{38}H_{49}F_2N_2O_3S_2$: 683.3153; found: 683.3132 (-3.0 ppm error).

10115

Example 1014

N-[4-(2-N-piperidin-1-ylaminoethenyl)-2-(2-methylphenyl)benzoyl]methionine, lithium salt

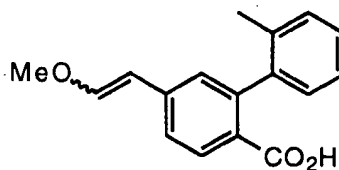
10120

Example 1014A

A solution of (methoxymethyl)triphenylphosphonium chloride (15.6 g, 45.6 mmol) in tetrahydrofuran solvent (35 mL) was treated with sodium bis(trimethylsilyl)amide (45 mL of a 1 M tetrahydrofuran solution, 45 mmol), and the resulting deep red solution was treated with 4-formyl-2-(2-methylphenyl)benzoic acid, methyl ester, 1332A (7.30 g, 28.7 mmol). After 18 h the reaction mixture was diluted with diethyl ether solvent (100 mL) and filtered through silica gel with additional diethyl ether rinses. Flash column chromatography eluting with hexane and ethyl acetate using an elution gradient of 98:2 to 94:6 afforded 6.62 g of 1014A as a white solid (82% yield).

1H NMR ($CDCl_3$): δ 2.06 (s, 3 H), 3.59 (s, 3 H), 3.70 (s, 3 H, E isomer), 3.79 (s, 3 H, Z isomer); 5.24 (d, $J = 7.1$ Hz, 1 H, Z isomer), 5.81 (d, $J = 13.2$ Hz, 1 H, E isomer), 6.23 (d, $J = 7.1$ Hz, 1 H, Z isomer), 7.06-7.10 (comp, 2 H), 7.16-7.64 (comp, 5 H), 7.90 (dd, $J = 2.3, 8.4$ Hz, 1 H). LR

MS (ESI $^+$): $(M+H)^+$ calc for $C_{18}H_{19}O_3$: 283; found: 283.

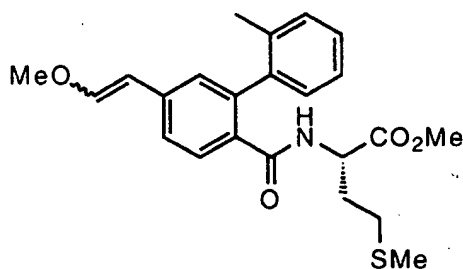


Example 1014B

10140 A solution of 1014A (2.42 g, 8.57 mmol) in saturated methanolic LiOH (10 mL) was heated to reflux for 16 h. The reaction mixture was poured into H₂O (90 mL), and the resulting mixture was extracted with diethyl ether (3 x 30 mL). The aqueous layer was cooled to 0 °C with vigorous stirring and was slowly and carefully neutralized and then acidified to pH 4 by the addition of 3 M HCl. The cloudy solution was extracted with diethyl ether (3 x 30 mL), and the combined organic extracts were dried over MgSO₄ and
 10145 then concentrated under reduced pressure to provide 1.81 g of 1014B as a white foam (79% yield). LR

MS (ESI⁺): (M+H)⁺ calc for C₁₇H₁₇O₃: 269; found: 269. LR

MS (ESI⁻): (M-H)⁻ calc for C₁₇H₁₅O₃: 267; found: 267.

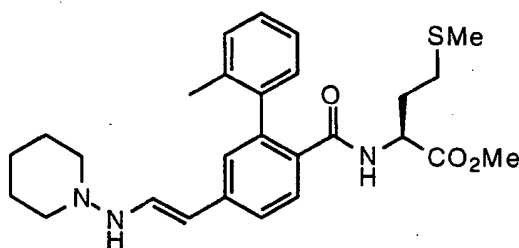


10150

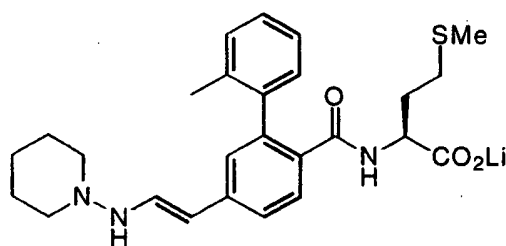
Example 1014C

A heterogeneous mixture of 1014B (1.81 g, 6.75 mmol), methionine methyl ester hydrochloride (2.72 g, 13.5 mmol), 1-hydroxybenzotriazole hydrate (HOBT) (4.56 g, 33.8 mmol), and 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide (EDC) (6.60 g, 33.8 mmol) in
 10155 DMF solvent (40 mL) was treated with triethylamine (3.45 g, 33.8 mmol). The mixture was heated to 50 °C for 60 h, cooled to room temperature, diluted with ethyl acetate (200 mL), and extracted with 2:1:1 H₂O: saturated aqueous NaHCO₃: brine (200 mL + 2 x 100 mL), followed by brine (50 mL). The organic layer was dried over MgSO₄ and then concentrated under reduced pressure to yield an amber oil. Flash column chromatography eluting with
 10160 hexane and ethyl acetate using an elution gradient of 80:20 to 70:30 afforded 2.55 g of 1014C as a colorless oil (91% yield).

¹H NMR (CDCl₃): δ 1.51-1.63 (m, 1 H), 1.79-1.91 (m, 1 H), 1.99-2.21 (comp, 8 H), 3.65 (s, 3 H), 3.70 (s, 3 H, E isomer), 3.79 (s, 3 H, Z isomer), 4.56-4.67 (m, 1 H), 5.24 (d, J = 7.1 Hz, 1 H, E isomer), 5.82 (d, J = 12.9 Hz, 1 H, E isomer), 5.83-5.89 (m, 1 H),
 10165 7.00-7.36 (comp, 6 H), 7.12 (d, J = 12.9 Hz, 1 H, E isomer), 7.63-7.96 (comp, 1 H). LR MS (ESI⁺): (M+H)⁺ calc for C₂₃H₂₈O₄S: 414; found: 414.

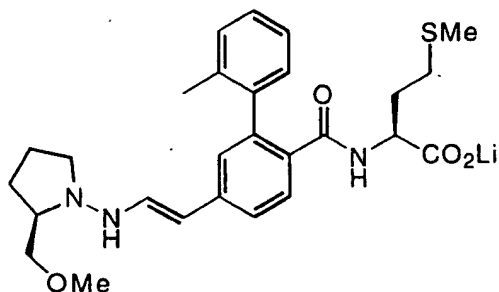
Example 1014D

- 10170 A solution of 1014C (8.0 mL of a 0.1 M dioxane solution, 0.800 mmol) and H₂O (1.6 mL) was treated with p-toluenesulfonic acid hydrate (0.0309 g, 0.160 mmol). After 17 h the mixture was diluted with additional H₂O (12 mL) and then extracted with ethyl acetate (10 mL + 3 x 5 mL). The combined organic extracts were rinsed with brine (5 mL), dried over MgSO₄, and concentrated under reduced pressure to provide a pale yellow oil. The oil
- 10175 was dissolved in benzene solvent (4 mL) and treated with Na₂SO₄ (0.454 g, 3.20 mmol), followed by 1-aminopiperidine (0.0991 g, 0.960 mmol), resulting in a bright yellow solution. After 18 h the reaction mixture was filtered through silica gel with ethyl acetate rinses and then concentrated under reduced pressure. Radial chromatography eluting with hexane and ethyl acetate using an elution gradient of 70:30 to 30:70 afforded 0.0342 g of
- 10180 1014D as a colorless oil (8.9% yield).
¹H NMR (CDCl₃): δ 1.44-1.53 (comp, 2 H), 1.54-1.74 (comp, 5 H), 1.79-1.91 (m, 1 H), 1.99-2.10 (comp, 5 H), 2.18 (s, 1 H), 2.95 (app t, J = 5.6 Hz, 4 H), 3.62-3.67 (comp, 5 H), 4.56-4.67 (m, 1 H), 5.88 (d, J = 7.8 Hz, 1 H), 6.93-6.99 (m, 1 H), 7.06 (s, 1 H), 7.16-7.35 (comp, 6 H), 7.91 (dd, J = 8.2, 15.6 Hz, 1 H). LR
- 10185 MS (ESI⁺): (M+H)⁺ calc for C₂₇H₃₆N₂O₃S: 482; found: 482. LR
 MS (ESI⁻): (M-H)⁻ calc for C₂₇H₃₄N₃O₃S: 480; found: 480.

Example 1014E

- 10190 N-[4-(2-N-piperidin-1-ylaminoethenyl)-2-(2-methylphenyl)benzoyl]methionine, lithium salt
 Compound 1014E was prepared in the same fashion as 997D (39% yield).
¹H NMR (d₆-DMSO): δ 1.36-1.45 (comp, 2 H), 1.50-1.76 (comp, 6 H), 1.76-2.20 (comp, 8 H), 2.84-2.90 (comp, 4 H), 3.53 (d, J = 5.8 Hz, 1 H), 3.62-3.72 (br, 1 H), 6.92 (d, J = 5.8 Hz, 1 H), 6.96-7.03 (comp, 2 H), 7.10-7.24 (comp, 4 H), 7.27 (dd, J = 1.4, 7.8 Hz, 1 H), 7.48 (d, J = 8.1 Hz, 1 H). HR
- 10195

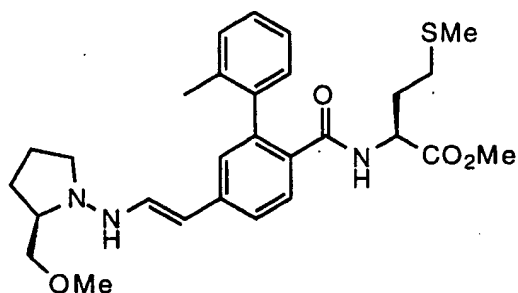
MS (FAB): (M+Li)⁺ calc for C₂₆H₃₃LiN₃O₃S: 474.2403; found: 474.2386 (-3.6 ppm error).



10200

Example 1015

N-[4-(2-N-2-methoxymethylpyrrolidin-1-ylaminoethenyl)-2-(2-methylphenyl)benzoyl]methionine, lithium salt



10205

Example 1015A

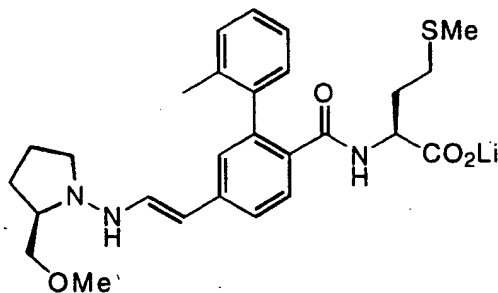
Compound 1015A was prepared in the same fashion as 1014D (11% yield).

¹H NMR (CDCl₃): δ 1.52-1.64 (m, 1 H), 1.71-2.20 (comp, 14 H), 2.72-2.84 (m, 1 H), 3.31-3.67 (comp, 12 H), 4.56-4.68 (m, 1 H), 5.88 (d, J = 7.3 Hz, 1 H), 6.64-6.70 (m, 1 H), 7.07 (s, 1 H), 7.17-7.35 (comp, 6 H), 7.91 (dd, J = 7.7, 15.4 Hz, 1 H). LR

10210

MS (ESI⁺): (M+H)⁺ calc for C₂₈H₃₈N₃O₄S: 512; found: 512. LR

MS (ESI⁻): (M-H)⁻ calc for C₂₈H₃₆N₃O₂S: 510; found: 510.



10215

Example 1015B

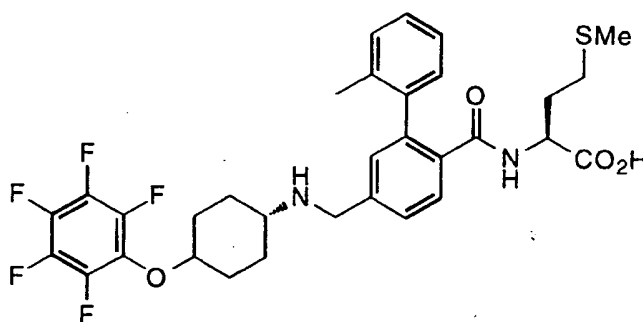
N-[4-(2-N-2-methoxymethylpyrrolidin-1-ylaminoethenyl)-2-(2-methylphenyl)benzoyl]methionine, lithium salt

Compound 1015B was prepared in the same fashion as 997D (50% yield).

¹H NMR (d₆-DMSO): δ 1.49-1.72 (comp, 3 H), 1.76-2.20 (comp, 10 H), 2.62-2.72 (m, 1 H), 3.19-3.55 (comp, 2 H), 3.62-3.74 (br, 1 H), 6.66 (app t, J = 5.5 Hz, 1 H), 6.89-6.94 (d, J = 5.5 Hz, 1 H), 7.02 (s, 1 H), 7.12-7.30 (comp, 5 H), 7.49 (d, J = 8.1 Hz, 1 H).

HR

MS (FAB): (M+Li)⁺ calc for C₂₇H₃₅LiN₃O₄S: 504.2508; found: 504.2509 (1.2 ppm error).



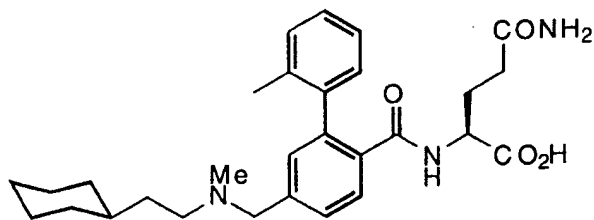
Example 1017

N-[4-N-(4-trans-pentafluorophenoxy)aminomethyl]-2-(2-methylphenyl)benzoyl]methionine

A solution of trans-4-aminocyclohexanol (3.03 g, 20.0 mmol) and diisopropylethylamine (7.4 mL, 42.0 mmol) in methylene chloride (30 mL) was treated with t-butyl dicarbonate (4.37 g, 20.0 mmol) over 5 minutes. The reaction stirred overnight at room temperature and was washed with 1 M HCl, 5% NaHCO₃, and brine to give the Boc-amine in nearly quantitative yield. A portion of this product (215 mg, 1.0 mmol) was combined with hexafluorobenzene (223 mg, 1.2 mmol) and 15-crown-5 (44 mg, 0.2 mmol) in DMF (3 mL) at room temperature. NaH (60% in oil, 4.4 mg, 1.2 mmol) was added and stirred overnight. Standard aqueous workup provided 149 mg of the protected pentafluorophenyl ether which was treated with excess TFA in methylene chloride, stripped to dryness, and reductively alkylated and saponified as described previously to provide 160 mg of the title compound.

MS m/e 635 (M-H)⁻.

¹H NMR (CDCl₃, 300 MHz) δ 1.5 (m, 4H), 1.79 (m, 1H), 2.05 (m, 12H), 2.81 (m, 1H), 4.05 (m, 4H), 6.25 (m, 1H), 6.81 (m, 2H), 7.1-7.7 (m, 7H).

**Example 1018**

N-[4-(N-(2-cyclohexylethyl)-N-methylaminomethyl)-2-(2-methylphenyl)benzoyl]glutamine

10250

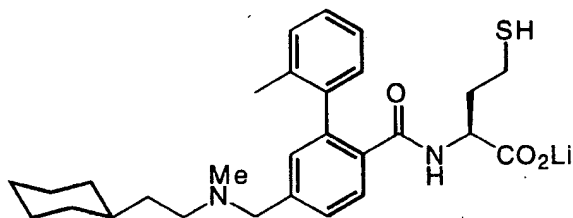
Trifluoroacetic Acid salt

The compound was made by standard amino acid coupling of 4-(N-(2-cyclohexylethyl)-N-methylaminomethyl)-2-(2-methylphenyl)benzoic acid and L-Glu-OtBu followed by treatment with TFA.

MS m/e 492 (M-H)⁻.

10255

¹H NMR (d₆-DMSO, 300 MHz) δ 0.91 (m, 2H), 1.1 (m, 4H), 1.63 (m, 9H), 1.9 (m, 3H), 2.1 (m, 3H), 2.71 (s, 3H), 3.1 (m, 2H), 4.09 (m, 1H), 4.29 (m, 1H), 4.43 (m, 1H); 6.74 (s, 1H), 7.1-7.22 (m, 3H), 7.39 (s, 1H), 7.60 (m, 2H), 8.32 (m, 2H), 9.62 (bs, 1H).



10260

Example 1019

N-[4-(N-(2-cyclohexylethyl)-N-methylaminomethyl)-2-(2-methylphenyl)benzoyl]homocysteine, lithium salt

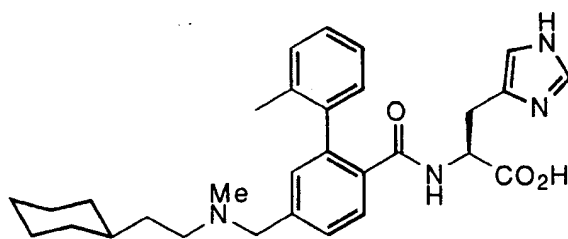
Prepared in a manner analogous to Example 1018 using L-homocysteine thiolactone and opening the resulting thiolactone with 1 equivalent of LiOH.

10265

MS m/e 481 (M-H)⁻.

¹H NMR (d₆-DMSO, 300 MHz) δ 0.84 (m, 2H), 1.11 (m, 3H), 1.32 (m, 5H), 1.6 (m, 7H), 2.18 (m, 7H), 3.48 (s, 3H), 3.82 (m, 1H), 3.97 (m, 1H), 6.95 (m, 1H), 7.0-7.34 (m, 4H), 7.5 (m, 1H), 7.65 (m, 1H), 8.39 (m, 1H).

10270

Example 1020

N-[4-(N-(2-cyclohexylethyl)-N-methylaminomethyl)-2-(2-methylphenyl)benzoyl]histidine

10275

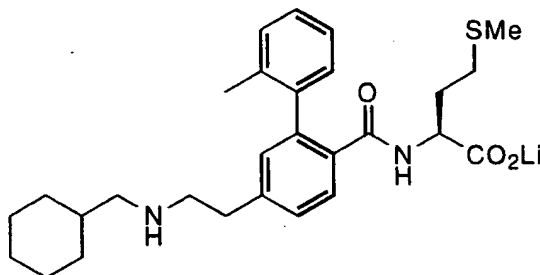
Trifluoroacetic Acid salt

Prepared in a manner analogous to Example 1018 using L-His(trt)-OMe•HCl, removing the methyl ester with LiOH, and removing the im-trityl group with TFA/triethylsilane.

MS m/e 497 (M+H)⁺.

10280

¹H NMR (d₆-DMSO, 300 MHz) δ 0.90 (m, 2H), 1.17 (m, 4H), 1.63 (m, 8H), 1.99 (m, 6H), 2.1 (m, 3H), 2.73 (m, 3H), 3.0 (m, 2H), 4.3 (m, 1H), 4.4 (m, 1H), 4.56 (m, 2H), 7.08 (m, 1H), 7.15-7.42 (m, 3H), 7.58 (m, 2H), 8.62 (m, 1H), 8.97 (s, 1H).



10285

Example 1021

N-[4-(N-(cyclohexylmethyl)aminoethyl)-2-(2-methylphenyl)benzoyl]methionine, lithium salt

N-[4-(N-(cyclohexylmethyl)aminoethyl)-2-(2-methylphenyl)benzoyl] methionine methyl ester (84 mg, 0.17 mmol) was treated with LiOH (1 M, 85 μL) in methanol to provide the title compound.

10290

MS m/e 481 (M-H)⁻.

¹H NMR (d₆-DMSO, 300 MHz) δ 0.83 (m, 2H), 1.15 (m, 4H), 1.36 (m, 1H), 1.62 (m, 9H), 1.98 (m, 10H), 3.7 (m, 2H), 4.27 (m, 1H), 6.90 (m, 1H), 7.00 (m, 1H), 7.1-7.3 (m, 4H), 7.44 (m, 1H), 8.24 (m, 1H).

10295

N-[4-(N-(cyclohexylmethyl)aminoethyl)-2-(2-methylphenyl)benzoyl] methionine methyl ester

Methyl 4-(N-(cyclohexylmethyl)aminoethyl)-2-(2-methylphenyl)benzoate hydrochloride (1.33 g, 3.31 mmol) was treated with sat. LiOH (1.3 mL, 6.95 mmol) in 50 mL methanol at 60 °C until no starting material remained by tlc. The solution was evaporated to dryness and treated with Met-OMe•HCl (0.99 g, 4.96 mmol), EDAC (1.26 g, 6.6 mmol), HOBt (1.5 g, 9.9 mmol), and TEA (to pH 6~7) in 25 mL DMF. Standard aqueous workup followed by flash chromatography (100 % EtOAc) provided 1.5 g of the title compound.

MS m/e 497 (M-H)⁻.

¹H NMR (CDCl₃, 300 MHz) δ 0.88 (m, 2H), 1.2 (m, 4H), 1.6 (m, 8H), 2.1 (m, 8H), 2.47 (m, 2H), 2.9 (m, 4H), 3.68 (s, 3H), 4.63 (m, 1H), 5.89 (d, 1H, J = 7 Hz), 7.04 (s, 1H), 7.19 (m, 1H), 7.3 (m, 4H), 7.91 (m, 1H).

Methyl 4-(N-(cyclohexylmethyl)aminoethyl)-2-(2-methylphenyl)benzoate

Methyl 4-(propan-3-yl)-2-(2-methylphenyl)benzoate (5.0 g, 18.6 mmol) and cyclohexylmethylamine (2.32 g, 10.5 mmol) were dissolved in 250 mL 1 % acetic acid in methanol. After 10 minutes, sodium cyanoborohydride (1.76 g, 28 mmol) was added. The mixture stirred overnight at room temperature before evaporating to dryness. The residue was dissolved in ether and washed with 5 % NaHCO₃, water, and brine, dried over Na₂SO₄, and treated with anh. HCl. The oily product was crystalized from methanol and ether.

MS m/e 366 (M+H)⁺.

¹H NMR (CDCl₃, 300 MHz) δ 0.88 (m, 2H), 1.2 (m, 4H), 1.6 (m, 6H), 2.06 (s, 3H), 2.48 (d, 2H, J = 7 Hz), 2.92 (s, 4H), 3.61 (s, 3H), 7.06 (m, 1H), 7.23 (m, 5H), 7.92 (m, 1H).

Methyl 4-(propan-3-yl)-2-(2-methylphenyl)benzoate

Methyl 4-(prop-2-enyl)-2-(2-methylphenyl)benzoate (5.23 g, 19.6 mmol), osmium tetroxide (0.02 mmol/mL t-BuOH, 29.5 mL), and sodium periodate (10.5 g, 49.1 mmol) were combined in 200 mL acetone with 50 mL water. After stirring at ambient temperature for 1 hour, the mixture was diluted with water and extracted with EtOAc. The combined organic extracts were washed with brine and dried over Na₂SO₄ to give the desired product which was used directly in the next step.

MS m/e 286 (M+NH₄)⁺.

¹H NMR (CDCl₃, 300 MHz) δ 2.06 (m, 3H), 3.61 (s, 3H), 3.8 (m, 2H), 7.1 (m, 1H), 7.25 (m, 5H), 7.95 (m, 1H), 9.80 (m, 1H).

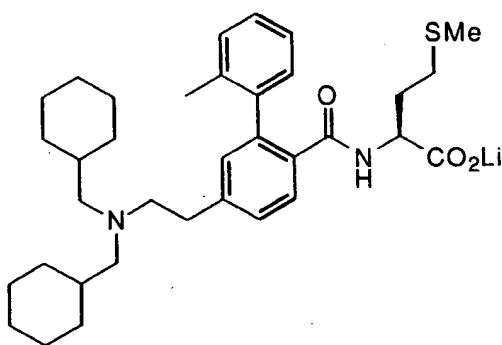
Methyl 4-(prop-2-enyl)-2-(2-methylphenyl)benzoate

10335 Methyl 4-iodo-2-(2-methylphenyl)benzoate (10.0 g, 28.4 mmol), allyltributyl tin (11.3 g, 34.1 mmol), and dichlorobis(triphenylphosphine)palladium (II) (1.0 g, 1.42 mmol) were combined in 50 mL toluene and 20 mL NMP and heated at 125 °C for 18 hours. The reaction was diluted with EtOAc, washed with water and brine, dried over Na₂SO₄, and chromatographed (5 % EtOAc in hexanes) to provide the title compound in 74 % yield.

MS m/e 284 (M+NH₄)⁺.

¹H NMR (CDCl₃, 300 MHz) δ 2.06 (s, 3H), 3.45 (d, 2H, J = 7 Hz), 3.61 (s, 3H), 5.1 (m, 2H), 5.97 (m, 1H), 7.08 (m, 1H), 7.23 (m, 5H), 7.94 (m, 1H).

10345



Example 1022

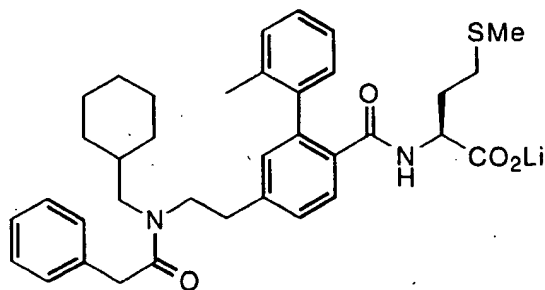
N-[4-(N,N-di-(cyclohexylmethyl)aminoethyl)-2-(2-methylphenyl)benzoyl]methionine,
lithium salt

10350 N-[4-(N-(cyclohexylmethyl)aminoethyl)-2-(2-methylphenyl)benzoyl] methionine methyl ester (300 mg, 0.60 mmol) and cyclohexylcarboxaldehyde (140 mg, 1.21 mmol) were dissolved in 1 % acetic acid in methanol (5 mL) and treated with sodium cyanoborohydride (76 mg, 1.21 mmol). Standard workup followed by flash chromatography (20 % ethyl acetate in hexane) provided 320 mg which was subsequently saponified with LiOH to the title compound.

MS m/e 577 (M-H)⁻.

¹H NMR (d₆-DMSO, 300 MHz) δ 0.75 (m, 4H), 1.10 (m, 8H), 1.30 (m, 2H), 1.61 (m, 9H), 2.0 (m, 10H), 2.6 (m, 2H), 2.7 (m, 2H), 3.3 (m, 1H), 3.68 (m, 1H), 6.90 (m, 2H), 7.1 (m, 5H), 7.44 (m, 1H).

10360



Example 1023

N-[4-(N-cyclohexylmethyl-N-phenylacetyl)aminoethyl]-2-(2-methylphenyl)benzoyl methionine, lithium salt

10365

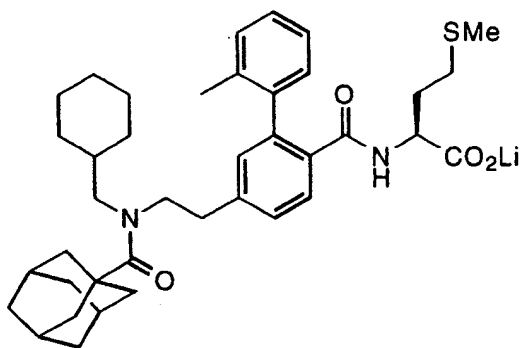
N-[4-(N-(cyclohexylmethyl)aminoethyl)-2-(2-methylphenyl)benzoyl methionine methyl ester (75 mg, 0.11 mmol), phenacetyl chloride (26 mg, 0.17 mmol), and triethylamine (17 mg, 0.15 mmol) were stirred in DMF (0.5 mL) for 18 hours at ambient temperature. The reaction was diluted with EtOAc, washed with 5 % NaHCO₃, water, and brine, dried over Na₂SO₄, and chromatographed (50 % EtOAc/hexanes) to provide 66 mg of the methyl ester of the title compound. This was subsequently saponified with LiOH in quantitative yield to the title compound.

10370

MS m/e 599 (M-H)⁻.

10375

¹H NMR (d₆-DMSO, 300 MHz) δ 0.83 (m, 2H), 1.15 (m, 4H), 1.6 (m, 9H), 1.98 (m, 8H), 2.8 (m, 1H), 3.1 (m, 2H), 3.5 (m, 3H), 3.7 (m, 2H), 7.0 (m, 2H), 7.1-7.3 (m, 9H), 7.45 (m, 1H).



Example 1024

N-[4-(N-cyclohexylmethyl-N-1-adamantanoyl)aminoethyl]-2-(2-methylphenyl)benzoyl methionine, lithium salt

10380

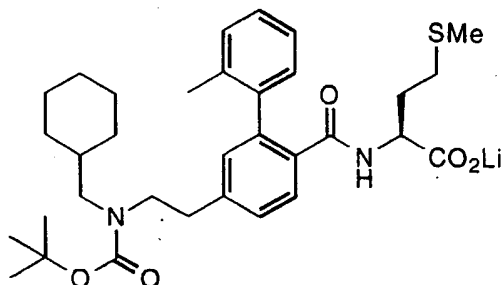
This compound was prepared in a manner analogous to Example 1023 using 1-adamantanecarbonyl chloride.

10385

MS m/e 643 (M-H)⁻.

^1H NMR (d_6 -DMSO, 300 MHz) δ 0.87 (m, 8H), 1.15 (m, 4H), 1.6 (m, 14H), 1.9 (m, 12H), 2.85 (m, 1H), 3.18 (m, 2H), 3.6 (m, 2H), 6.91 (m, 1H), 7.02 (m, 1H), 7.2 (m, 5H), 7.48 (m, 1H).

10390

Example 1025

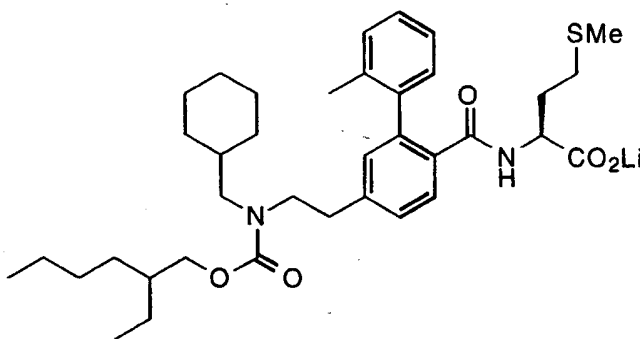
N-[4-(N-cyclohexylmethyl-N-t-butoxycarbonylaminoethyl)-2-(2-methylphenyl)benzoyl]methionine, lithium salt

10395 This compound was prepared in a manner analogous to Example 1023 using di-*t*-butyldicarbonate.

MS *m/e* 581 (M-H)⁻.

^1H NMR (d_6 -DMSO, 300 MHz) δ 0.83 (m, 2H), 1.15 (m, 4H), 1.38 (s, 9H), 1.6 (m, 9H), 1.95 (m, 6H), 2.18 (m, 2H), 2.8 (m, 4H), 3.7 (m, 1H), 6.9 (m, 1H), 7.0 (m, 1H), 7.2 (m, 5H), 7.45 (m, 1H).

10400

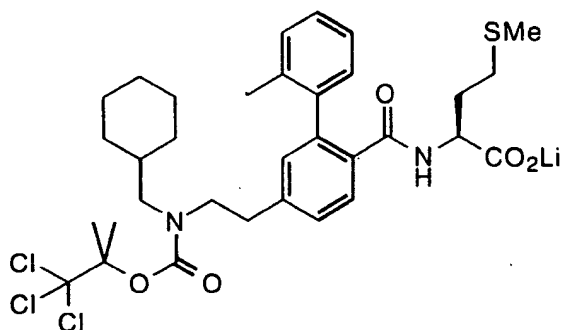
Example 1026

10405 N-[4-(N-cyclohexylmethyl-N-2-ethylhexyloxycarbonylaminoethyl)-2-(2-methylphenyl)benzoyl]methionine, lithium salt

This compound was prepared in a manner analogous to Example 1023 using 2-ethylhexyl chloroformate.

MS *m/e* 637 (M-H)⁻.

10410 ^1H NMR (d_6 -DMSO, 300 MHz) δ 0.83 (m, 4H), 1.15 (m, 4H), 1.23 (m, 9H), 1.6 (m, 9H), 1.95 (m, 8H), 2.83 (m, 2H), 3.0 (m, 2H), 3.5 (m, 3H), 3.6 (m, 1H), 3.89 (m, 2H), 4.29 (m, 1H), 6.9 (m, 1H), 7.0 (m, 1H), 7.2 (m, 5H), 7.45 (m, 1H).



10415

Example 1027

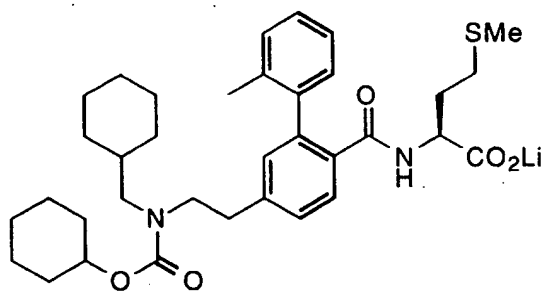
N-[4-(N-cyclohexylmethyl-N-2,2,2-trichloroethoxycarbonylaminoethyl)-2-(2-methylphenyl)benzoyl]methionine, lithium salt

This compound was prepared in a manner analogous to Example 1023.

10420 MS m/e 683 (M-H) $^-$.

^1H NMR (d_6 -DMSO, 300 MHz) δ 0.84 (m, 2H), 1.17 (m, 4H), 1.6 (m, 5H), 1.9 (m, 14H), 2.9 (m, 3H), 3.03 (m, 1H), 3.5 (m, 3H), 3.6 (m, 1H), 4.28 (m, 1H), 6.9 (m, 1H), 7.0 (m, 2H), 7.2 (m, 5H), 7.45 (m, 1H).

10425



Example 1028

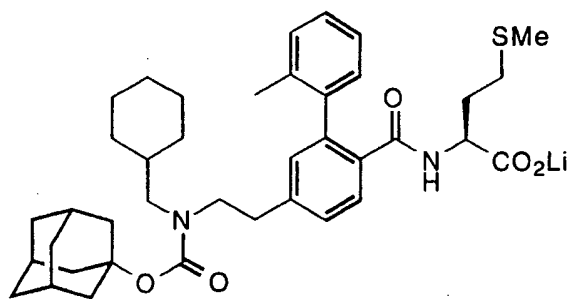
N-[4-(N-cyclohexylmethyl-N-cyclohexyloxycarbonylaminoethyl)-2-(2-methylphenyl)benzoyl]methionine, lithium salt

10430 This compound was prepared in a manner analogous to Example 1023.

MS m/e 607 (M-H) $^-$.

^1H NMR (d_6 -DMSO, 300 MHz) δ 0.84 (m, 4H), 1.17 (m, 4H), 1.3 (m, 6H), 1.6 (m, 10H), 1.95 (m, 8H), 2.17 (m, 1H), 2.9 (m, 4H), 3.6 (m, 1H), 4.53 (m, 1H), 6.9 (m, 1H), 7.0 (m, 1H), 7.2 (m, 5H), 7.47 (m, 1H).

10435

Example 1029

N-[4-(N-cyclohexylmethyl-N-adamantyloxycarbonylaminoethyl)-2-(2-
methylphenyl)benzoyl]methionine, lithium salt

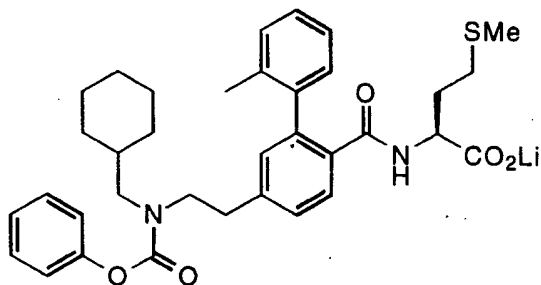
10440

This compound was prepared in a manner analogous to Example 1023.

MS m/e 659 (M-H)⁻.

¹H NMR (d₆-DMSO, 300 MHz) δ 0.83 (m, 6H), 1.16 (m, 6H), 1.6 (m, 13H), 2.0 (m, 12H), 2.82 (m, 3H), 2.95 (m, 1H), 3.65 (m, 2H), 6.95 (m, 2H), 7.2 (m, 5H), 7.47 (m, 1H).

10445

Example 1030

N-[4-(N-cyclohexylmethyl-N-phenoxy carbonylaminoethyl)-2-(2-
methylphenyl)benzoyl]methionine, lithium salt

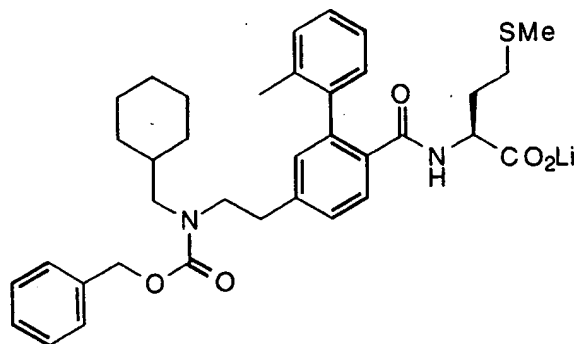
10450

This compound was prepared in a manner analogous to Example 1023.

MS m/e 601 (M-H)⁻.

¹H NMR (d₆-DMSO, 300 MHz) δ 0.91 (m, 2H), 1.19 (m, 4H), 1.63 (m, 9H), 1.98 (m, 6H), 2.15 (m, 2H), 2.97 (m, 1H), 3.11 (m, 1H), 3.5 (m, 1H), 3.7 (m, 2H), 6.85-7.39 (m, 12H), 7.48 (m, 1H).

10455



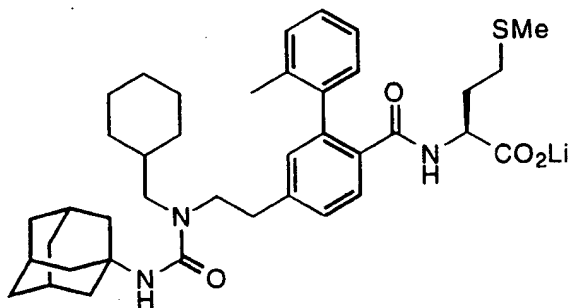
Example 1031

N-[4-(N-cyclohexylmethyl-N-benzyloxycarbonylaminoethyl)-2-(2-methylphenyl)benzoyl]methionine, lithium salt

This compound was prepared in a manner analogous to Example 1023.

MS m/e 615 (M-H)⁻.

¹H NMR (d₆-DMSO, 300 MHz) δ 0.83 (m, 2H), 1.13 (m, 4H), 1.6 (m, 6H), 1.95 (m, 6H), 2.14 (m, 2H), 2.83 (m, 2H), 2.99 (m, 2H), 3.40 (m, 2H), 3.65 (m, 2H), 5.04 (m, 2H), 6.9-7.3 (m, 12H), 7.43 (m, 1H).



Example 1032

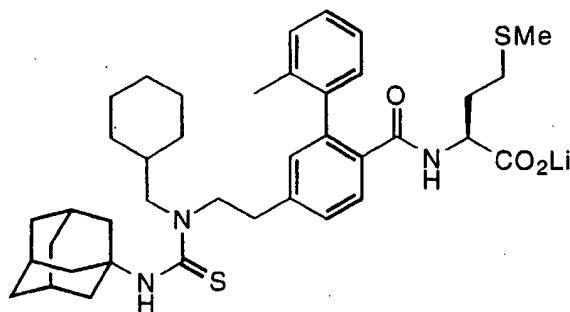
N-[4-(N-cyclohexylmethyl-N-adamant-1-aminocarbonylaminoethyl)-2-(2-methylphenyl)benzoyl]methionine, lithium salt

This compound was prepared in a manner analogous to Example 1023 using

adamantyl isocyanate.

MS m/e 658 (M-H)⁻.

¹H NMR (d₆-DMSO, 300 MHz) δ 0.83 (m, 6H), 1.13 (m, 6H), 1.6 (m, 13H), 1.95 (m, 12H), 2.18 (m, 1H), 2.79 (m, 2H), 2.91 (m, 2H), 3.65 (m, 2H), 6.9 (m, 1H), 7.0 (m, 1H), 7.2 (m, 5H), 7.46 (m, 1H).

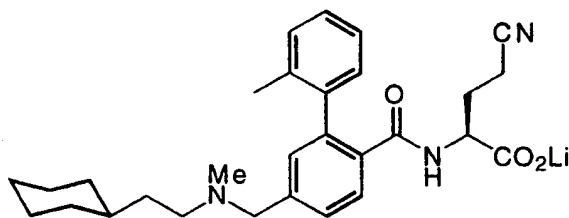
Example 1033

N-[4-(N-cyclohexylmethyl)-N-adamant-1-aminothiocarbonylaminoethyl]-2-(2-
methylphenyl)benzoyl]methionine, lithium salt

This compound was prepared in a manner analogous to Example 1023 using adamantyl isothiocyanate.

MS m/e 674 (M-H)⁻.

¹H NMR (d₆-DMSO, 300 MHz) δ 0.85 (m, 6H), 1.15 (m, 6H), 1.6 (m, 13H), 2.0 (m,
 12H), 2.2 (m, 1H), 2.74 (m, 2H), 2.91 (m, 2H), 3.62 (m, 2H), 6.9-7.5 (m, 8H).

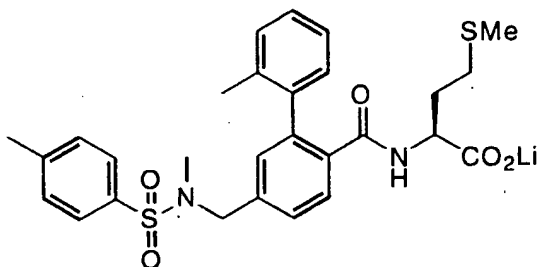
Example 1041

N-[4-(N-(2-cyclohexylethyl)-N-methylaminomethyl)-2-(2-
methylphenyl)benzoyl]glutaminitrile, lithium salt

Boc-Gln (2.0 g, 8.11 mmol) and acetic anhydride (0.92 mL, 9.7 mmol) were combined in dry pyridine (10 mL) and stirred at room temperature overnight. The solution was evaporated to dryness and partitioned between EtOAc and 10 % citric acid. The organic layer was washed with 10 % citric acid, water, and brine, dried over Na₂SO₄, and evaporated to dryness. The residue was dissolved in MeOH (5 mL) and treated with trimethylsilyldiazomethane (2.0 M in hexanes, excess). The mixture was evaporated and chromatographed (50 % EtOAc in hexanes) to give 0.92 g of Boc-glutaminitrile methyl ester. The nitrile (0.24 g, 1 mmol) was treated with excess 50 % trifluoroacetic acid in methylene chloride, evaporated and coupled to 4-(2-cyclohexylethyl-N-methylaminomethyl)-2-(2-methylphenyl)benzoic acid via standard techniques, followed by standard lithium hydroxide saponification to provide the title compound.

MS m/e 474 (M-H)⁻.

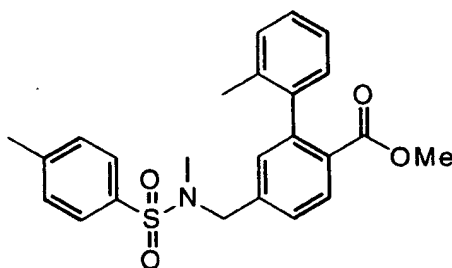
¹H NMR (d₆-DMSO, 300 MHz) δ 0.82 (m, 2H), 1.11 (m, 3H), 1.32 (m, 5H), 1.6 (m, 7H), 2.18 (m, 6H), 2.32 (m, 1H), 2.58 (m, 1H), 2.75 (m, 1H), 3.53 (m, 2H), 6.9-7.5 (m, 7H), 7.83 (m, 1H).



10515

Example 1047

N-[4-(N-p-Toluenesulfonyl-N-methylaminomethyl)-2-(2-methylphenyl)benzoyl]methionine, lithium salt



10520

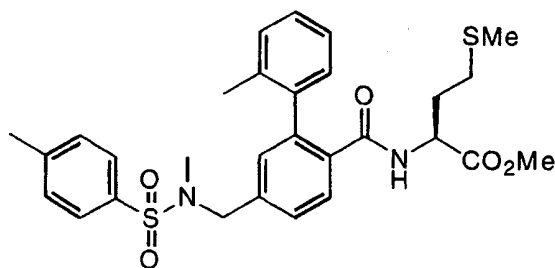
Example 1047A

4-(N-p-Toluenesulfonyl-N-methylaminomethyl)-2-(2-methylphenyl)benzoic acid, Methyl Ester

To a solution of N-methyl-p-toluenesulfonamide (203mg) and 4-hydroxymethyl-2-(2-methylphenyl)benzoic acid methyl ester (example 1178C, 255mg) in THF (3mL) at 0°C was added triphenylphosphine (315mg) and diethyl azodicarboxylate (0.19mL). The reaction was warmed, and stirred at ambient temperature for 30h. The reaction was concentrated, and the residue was purified by silica gel chromatography eluting with a gradient from 20% EtOAc/hexane to 100% EtOAc. The product was isolated as a colorless oil (170mg, 40%).

10530

MS (DCI/NH₃) 441 (M+NH₄)⁺.

Example 1047B

N-[4-(N-p-Toluenesulfonyl-N-methylaminomethyl)-2-(2-methylphenyl)benzoyl]methionine, Methyl Ester

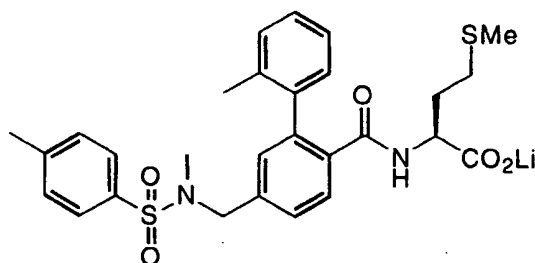
10535

4-(N-p-Toluenesulfonyl-N-methylaminomethyl)-2-(2-methylphenyl)benzoic acid methyl ester was converted to the title compound according to the procedures in examples 608C and D.

MS (APCI(+)) m/e (M+H)⁺ 555,

10540

MS (APCI(-)) m/e (M-H)⁻ 553.

Example 1047C

N-[4-(N-p-Toluenesulfonyl-N-methylaminomethyl)-2-(2-methylphenyl)benzoyl]methionine, lithium salt

10545

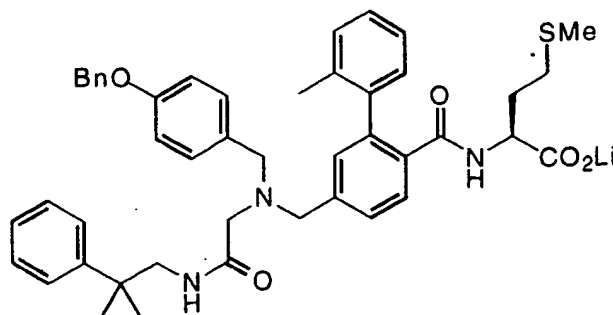
N-[4-(N-p-Toluenesulfonyl-N-methylaminomethyl)-2-(2-methylphenyl)benzoyl]methionine methyl ester was converted to the title compound by the procedure in example 608E. The product was isolated as a white powder.

10550

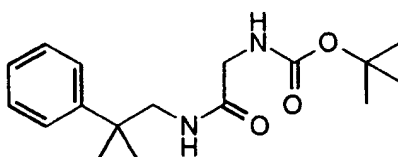
¹H NMR (300 MHz, DMSO) δ 1.50-1.88 (m, 4H), 1.92 (s, 3H), 1.95-2.14 (m, 3H), 2.41 (s, 3H), 2.59 (s, 3H), 3.58-3.70 (m, 1H), 4.18 (s, 2H), 6.96 (brd, J=5.4 Hz, 1H), 7.02-7.26 (m, 5H), 7.35 (d, J=8.1 Hz, 1H), 7.44 (d, J=7.8 Hz, 2H), 7.52 (d, J=8.1 Hz, 1H), 7.72 (d, J=7.8 Hz, 2H).

MS (ESI(-)) m/e 539 (M-H); Analysis calc'd for C₂₈H₃₁LiN₂O₅S₂•1.50H₂O: C, 58.63; H, 5.97; N, 4.88; found: C, 58.61; H, 5.66; N, 4.51.

10555

Example 1048

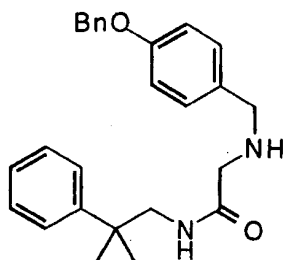
N-[4-(N-(4-Benzyloxybenzyl)-N-(N-2-methyl-2-phenylpropylacetamido)aminomethyl)-2-(2-methylphenyl)benzoyl]methionine, lithium salt

Example 1048A

N-(2-Methyl-2-phenylpropyl)-N-tert-butoxycarbonyl-2-aminoacetamide

To a slurry of NaH (10g of a 60% dispersion in mineral oil) in dry THF (300mL) was added benzyliocyanide (10g) by means of a dropping funnel. Cautious addition of methyl iodide (13mL) caused rapid gas evolution and an increase in temperature which was moderated with an ice bath. After stirring at ambient temperature for 12h, the reaction was quenched cautiously with water (100mL). The mixture was diluted with ether (500mL) and the layers were separated. The ether layer was washed with water (100mL) containing a small amount of Na₂SO₃ to eliminate the iodine color, then washed with brine (50mL). The organic solution was dried (MgSO₄), filtered and concentrated to afford an oil. This material was added neat to a solution of 1M LiAlH₄ (85mL, THF) in ether (100mL). If necessary, the reduction was initiated after a small amount of starting material was added by warming with a heat gun. The starting material was then added at a rate which maintained a gentle reflux. After addition was complete, the reaction was stirred without heating or cooling for 1h. The reaction was cautiously quenched with vigorous stirring by the addition of water (3.2mL), 15%NaOH (3.2mL), and more water (10mL). The suspension was filtered through celite, which was rinsed with ether. The filtrate was concentrated to give an oil (ca. 20g) which contained mineral oil from the sodium hydride dispersion. A portion of this material (3.3g) was dissolved in DMF (67mL) along with N-(tert-butoxycarbonyl)glycine (3.5g), followed by addition of N-methylmorpholine (3.3mL), 1-hydroxybenzotriazole (3.0g), and 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide (5.0g). After stirring at ambient temperature for 15h, the reaction was poured into ether (500mL), washed with water

10585 (2X100mL), 1M HCl (2X100mL), saturated NaHCO₃ (2X50mL), and brine (100mL). The organic solution was dried (MgSO₄), filtered and concentrated to afford a residue which partly solidified. The residue was triturated with hexane, and filtered to give 4.5g of the title compound. MS(DCI/NH₃) 307 (M+H)⁺.

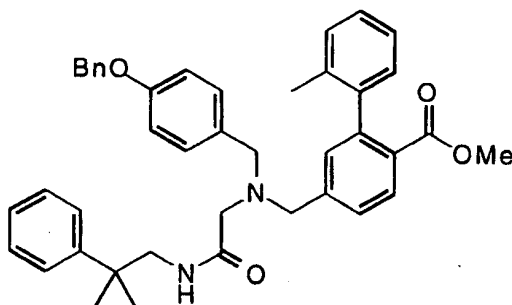


10590

Example 1048B

N-(2-Methyl-2-phenylpropyl)-N-(4-benzyloxybenzyl)-2-aminoacetamide

To a solution of N-(2-methyl-2-phenylpropyl)-N-tert-butoxycarbonyl-2-aminoacetamide (4.5g) in dichloromethane (50mL) was added trifluoroacetic acid (10mL).
10595 After 1.5h at ambient temperature, the reaction was concentrated, then the residue was evaporated from toluene to afford a light tan solid (4.4g). This material was stirred with 4-benzyloxybenzaldehyde (3.27g) in 1:1 THF:EtOH (30mL). Bromocresol green (1mg) was added, and the reaction was adjusted to pH≈3 with 15%NaOH. The reaction was warmed briefly to reflux to complete dissolution of starting material, then cooled to ambient
10600 temperature. Sodium cyanoborohydride (15mL, 1M THF) was added, and the reaction color was held at a light green by addition of a 2:1 ethanol:HCl mixture. After starting aldehyde was consumed (TLC), the reaction was concentrated, dissolved in EtOAc (200mL), and washed with saturated NaHCO₃ (2X50mL), water (50mL), and brine (50mL). The organic solution was dried (MgSO₄), filtered and concentrated, and the residue
10605 was purified by silica gel chromatography to give the title compound (1.96g) along with a significant amount of double alkylation product. MS(ESI) 403 (M+H)⁺.

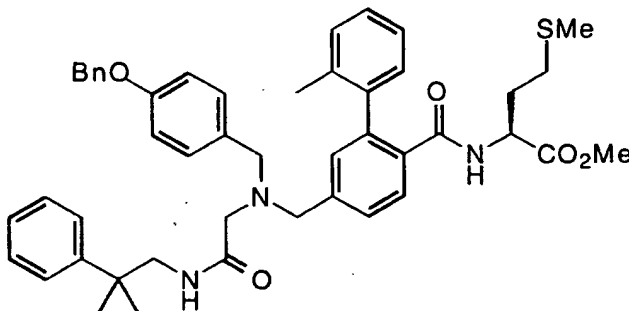


Example 1048C

10610 4-(N-(4-Benzyloxybenzyl)-N-(N-2-methyl-2-phenylpropylacetamido)aminomethyl)-2-(2-methylphenyl)benzoic acid, Methyl Ester

The title compound was prepared by the procedure in example 608B, replacing N-methylcyclohexylethylamine with N-(2-methyl-2-phenylpropyl)-N-(4-benzyloxybenzyl)-2-aminoacetamide. MS(APCI(+)) 641 (M+H)⁺. MS(APCI(-)) 675 (M+Cl)⁻.

10615

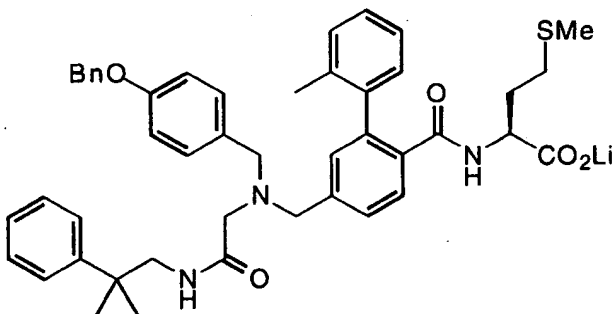


Example 1048D

N-[4-(N-(4-Benzyloxybenzyl)-N-(N-2-methyl-2-phenylpropylacetamido)aminomethyl)-2-(2-methylphenyl)benzoyl]methionine, Methyl Ester

10620

4-(N-(4-Benzyloxybenzyl)-N-(N-(2-methyl-2-phenylpropylamino)acetylaminomethyl)-2-(2-methylphenyl)benzoic acid methyl ester was converted to the title compound according to the procedures in examples 608C and D. MS(APCI(+)) 772 (M+H)⁺. MS(APCI(-)) 806 (M+Cl)⁻.



10625

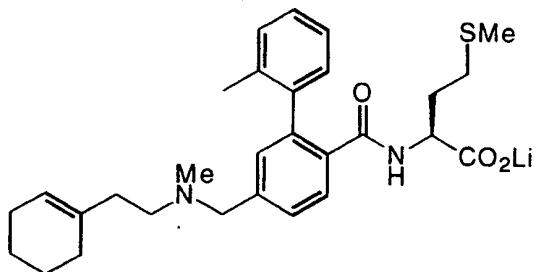
Example 1048E

N-[4-(N-(4-Benzyloxybenzyl)-N-(N-2-methyl-2-phenylpropylacetamido)aminomethyl)-2-(2-methylphenyl)benzoyl]methionine, lithium salt

10630 N-[4-(N-(4-Benzyloxybenzyl)-N-(N-(2-methyl-2-phenylpropylamino)acetylaminomethyl)-2-(2-methylphenyl)benzoyl]methionine methyl ester was converted to the title compound by the procedure in example 608E. The product was isolated as a white powder.

¹H NMR (300 MHz, DMSO) δ 1.15 (s, 3H), 1.16 (s, 3H), 1.50-1.84 (m, 5H), 1.92 (s, 3H), 1.95-2.16 (m, 3H), 2.88 (s, 2H), 3.28 (s, 2H), 3.39 (s, 2H), 3.47 (s, 2H), 3.60-

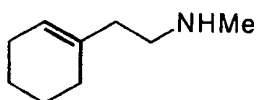
10635 3.68 (m, 1H), 5.07 (s, 2H), 6.87 (d, J=9 Hz, 2H), 6.93 (d, J=9 Hz, 2H), 6.93-7.48 (m, 17H). Analysis calc'd for $C_{46}H_{50}LiN_3O_5S \cdot 1.95H_2O$: C, 69.15; H, 6.80; N, 5.26; found: C, 69.11; H, 6.50; N, 5.13.



10640

Example 1056

N-[4-(N-(2-Cyclohexenylethyl)-N-methylaminomethyl)-2-(2-methylphenyl)benzoyl]methionine, lithium salt



10645

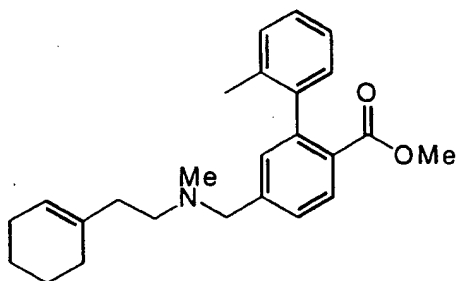
Example 1056A

N-Methyl-2-(1-cyclohexenyl)ethylamine

To a solution of 2-(1-cyclohexenyl)ethylamine (4.0g) in 1,4-dioxane (40mL) was added di-tert-butylidicarbonate (7.7g). After gas evolution ceased (≈ 2 h) the reaction was concentrated. A portion of the residue (2g) was dissolved in THF (10mL) followed by addition of $LiAlH_4$ (10mL, 1M THF), which caused an exotherm. After 3h, more $LiAlH_4$ solution was added (4mL), and the reaction was warmed to reflux. After 1h, the reaction was cooled, and quenched cautiously with vigorous stirring by the addition of water (0.57mL), 1M NaOH (0.6mL), and more water (1.5mL). The suspension was filtered through celite, which was washed with ether. The organic solution was concentrated to give the desired product as a volatile oil (0.8g).

10655

1H NMR (300 MHz, $CDCl_3$) δ 1.52-1.67 (m, 4H), 1.89-2.04 (m, 4H), 2.14 (brt, J=7 Hz, 2H), 2.42 (s, 3H), 2.63 (t, J=7 Hz, 2H), 5.45 (m, 1H).

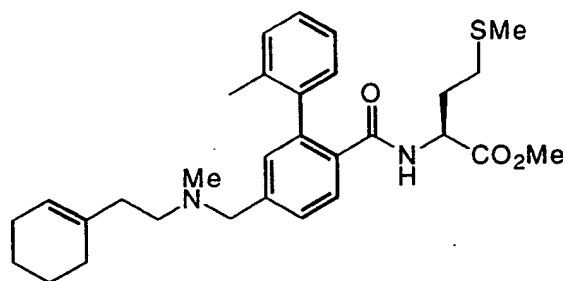


10660

Example 1056B4-(N-(2-Cyclohexenylethyl)-N-methylaminomethyl)-2-(2-methylphenyl)benzoic acid,Methyl Ester

The title compound was prepared from N-methyl-2-(1-cyclohexenyl)ethanamine according to the procedure in example 608B.

10665

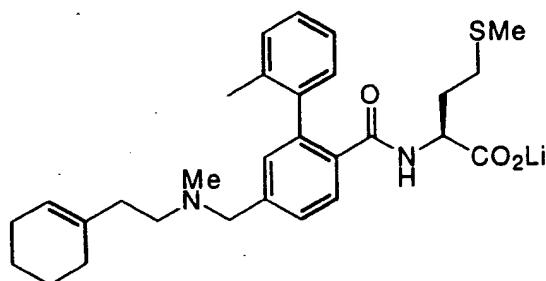
MS (DCI/NH₃) 378 (M+H)⁺.Example 1056C

10670

N-[4-(N-(2-Cyclohexenylethyl)-N-methylaminomethyl)-2-(2-methylphenyl)benzoyl]methionine, Methyl Ester

The title compound was prepared from 4-(N-(2-cyclohexenylethyl)-N-methylaminomethyl)-2-(2-methylphenyl)benzoic acid methyl ester according to the procedure in examples 608C and D. MS(APCI(+)) 509 (M+H)⁺. MS(APCI(-)) 543 (M+Cl)⁻.

10675

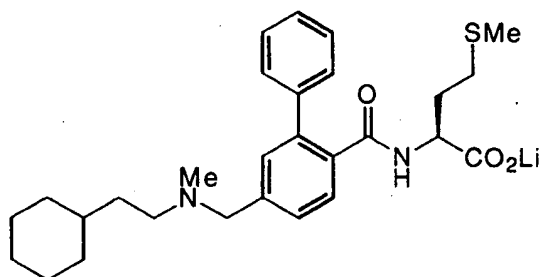
Example 1056D

N-[4-(N-(2-Cyclohexenylethyl)-N-methylaminomethyl)-2-(2-methylphenyl)benzoyl]methionine, lithium salt

10680

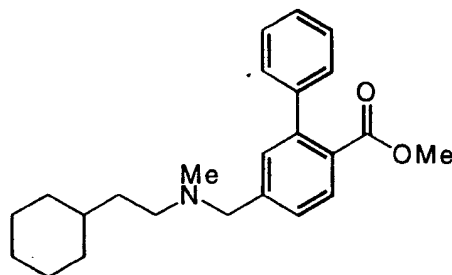
N-[4-(N-(2-Cyclohexenylethyl)-N-methylaminomethyl)-2-(2-methylphenyl)benzoyl]methionine methyl ester was converted into the title compound by the procedure in example 608E, and was isolated as a white powder.

¹H NMR (300 MHz, DMSO) δ 1.38-1.75 (m, 4H), 1.80-2.13 (m, 13H), 1.91 (s, 3H), 2.14 (s, 3H), 2.36-2.45 (m, 2H), 3.50 (s, 2H), 3.56-3.67 (brs, 1H), 5.32-5.36 (m, 1H), 6.88-6.92 (m, 1H), 7.05-7.23 (m, 5H), 7.32 (d, J=8.1 Hz, 1H), 7.48 (d, J=8.1 Hz, 1H). MS (APCI(-)) m/e 493 (M-H); Analysis calc'd for C₂₉H₃₇LiN₂O₃S•1.15H₂O: C, 66.81; H, 7.60; N, 5.37; found: C, 66.86; H, 7.34; N, 5.19.



Example 1057

N-[4-(N-(2-Cyclohexylethyl)-N-methylaminomethyl)-2-phenylbenzoyl]methionine, lithium salt

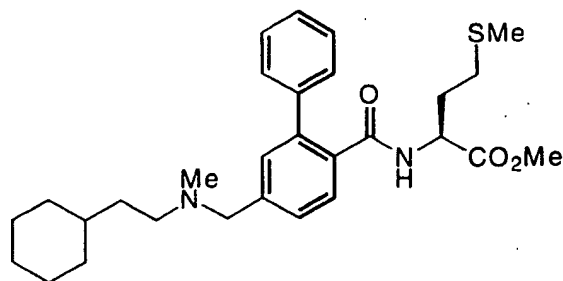


Example 1057A

4-(N-(2-Cyclohexylethyl)-N-methylaminomethyl)-2-phenylbenzoic acid, Methyl Ester

The title compound was prepared according to the procedure in example 608B, replacing 4-bromomethyl-2-(2-methylphenyl)benzoic acid methyl ester with 4-bromomethyl-2-phenylbenzoic acid methyl ester (example 228B).

MS (DCI/NH₃) 366 (M+H)⁺.



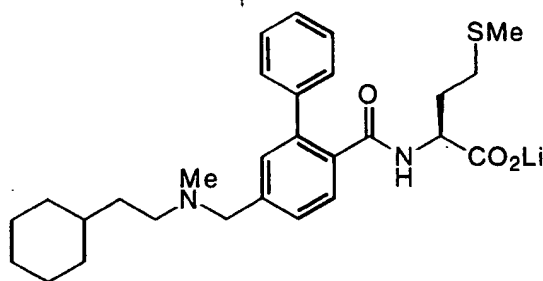
10705

Example 1057B

N-[4-(N-(2-Cyclohexylethyl)-N-methylaminomethyl)-2-phenylbenzoyl]methionine, Methyl Ester

The title compound was prepared from 4-(N-(2-cyclohexylethyl)-N-methylaminomethyl)-2-phenylbenzoic acid methyl ester according to the procedure in examples 608C and D. MS(APCI(+)) 497 (M+H)⁺. MS(APCI(-)) 531 (M+Cl)⁻.

10710

Example 1057C

N-[4-(N-(2-Cyclohexylethyl)-N-methylaminomethyl)-2-phenylbenzoyl]methionine, lithium salt

10715

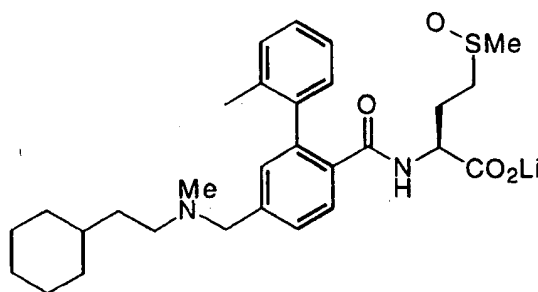
N-[4-(N-(2-Cyclohexylethyl)-N-methylaminomethyl)-2-phenylbenzoyl]methionine methyl ester was converted into the title compound according to the procedure in example 608E, and was isolated as a white powder.

¹H NMR (300 MHz; DMSO) δ 0.76-0.92 (m, 2H), 1.06-1.38 (m, 5H), 1.53-1.67 (m, 6H), 1.67-1.89 (m, 2H), 1.97 (s, 3H), 1.98-2.20 (m, 2H), 2.14 (s, 3H), 2.36 (t, J=6 Hz, 2H), 3.51 (s, 2H), 3.76-3.82 (m, 1H), 7.16 (d, J=6 Hz, 1H), 7.27-7.41 (m, 8H).

10720

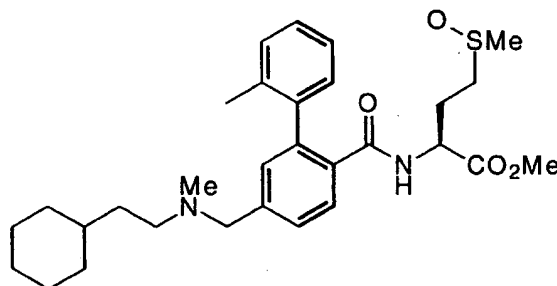
MS (APCI(-)) m/e 481 (M-H); Analysis calc'd for C₂₈H₃₇LiN₂O₃S•0.95H₂O: C, 66.50; H, 7.75; N, 5.54; found: C, 66.53; H, 7.58; N, 5.47.

10725

Example 1058

(2S) 2-N-[4-(N-(2-Cyclohexylethyl)-N-methylaminomethyl)-2-(2-methylphenyl)benzoyl]amino-4-methylsulfenylbutanoate, lithium salt

10730

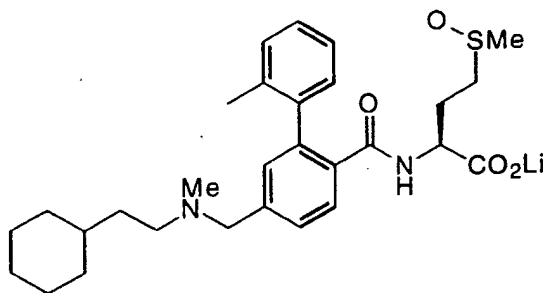
Example 1058A

(2S) 2-N-[4-(N-(2-Cyclohexylethyl)-N-methylaminomethyl)-2-(2-methylphenyl)benzoyl]amino-4-methylsulfenylbutanoic acid, Methyl Ester

10735

To a solution of N-[4-(N-(2-cyclohexylethyl)-N-methylaminomethyl)-2-(2-methylphenyl)benzoyl]methionine methyl ester (example 608D, 100mg) in dichloromethane (2mL) at ambient temperature was added trifluoroacetic acid (0.023ml), and the salt solution was cooled to 0°C. Hydrogen peroxide (30%, 0.050mL) was added with vigorous stirring. After 42h at ambient temperature, the reaction was concentrated and the residue was purified by silica gel chromatography eluting with 2.5%-5.0%-10.0% MeOH/CH₂Cl₂, to give two products which were both colorless oils. The more mobile product is (2S) 2-N-[4-(N-(2-cyclohexylethyl)-N-methylaminomethyl)-2-(2-methylphenyl)benzoyl]amino-4-methylsulfonylbutanoic acid methyl ester (35mg, 33%). MS(APCI(+)) 543 (M+H)⁺. MS(APCI(-)) 577 (M+Cl)⁻. The less mobile product is the title compound (50mg, 48%). MS(APCI(+)) 527 (M+H)⁺. MS(APCI(-)) 561 (M+Cl)⁻.

10745

**Example 1058B**

(2S) 2-N-[4-(N-(2-Cyclohexylethyl)-N-methylaminomethyl)-2-(2-methylphenyl)benzoyl]amino-4-methylsulfonylbutanoate, lithium salt

10750

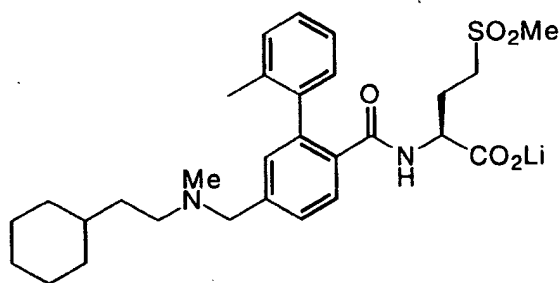
(2S) 2-N-[4-(N-(2-Cyclohexylethyl)-N-methylaminomethyl)-2-(2-methylphenyl)benzoyl]amino-4-methylsulfonylbutanoic acid methyl ester was converted to the title compound according to the procedure in example 608E, with the exception that the product was isolated as a white powder after trituration of the concentrated reaction residue with diethyl ether and drying under vacuum.

10755

¹H NMR (300 MHz, DMSO) δ 0.76-0.90 (m, 2H), 1.04-1.37 (m, 5H), 1.53-1.65 (m, 6H), 1.66-1.90 (m, 2H), 1.95-2.22 (m, 5H), 2.13 (s, 3H), 2.32 (t, J=7.2 Hz, 2H), 2.37 (s, 1.5H), 2.39 (s, 1.5H), 3.49 (s, 2H), 3.64-3.77 (m, 1H), 6.99 (d, J=6 Hz, 1H), 7.06-7.26 (m, 5H), 7.32 (d, J=7.5 Hz, 1H), 7.50 (d, J=8.1 Hz, 0.5H), 7.51 (d, J=8.1 Hz, 0.5H).

10760

MS (ESI(-)) m/e 511 (M-H).



10765

Example 1059

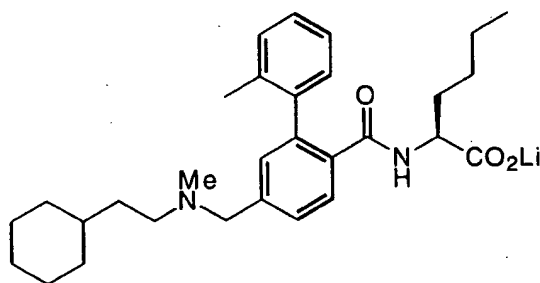
(2S) 2-N-[4-(N-(2-Cyclohexylethyl)-N-methylaminomethyl)-2-(2-methylphenyl)benzoyl]amino-4-methylsulfonylbutanoate, lithium salt

(2S) 2-N-[4-(N-(2-Cyclohexylethyl)-N-methylaminomethyl)-2-(2-methylphenyl)benzoyl]amino-4-methylsulfonylbutanoic acid methyl ester (example 1058A) was converted to the title compound according to the procedure in example 608E, with the exception that the product was isolated as a white powder after trituration of the concentrated reaction residue with diethyl ether and drying under vacuum.

10770

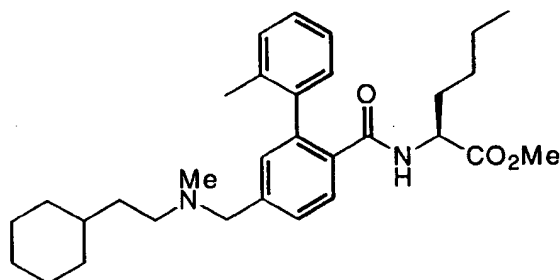
¹H NMR (300 MHz, DMSO) δ 0.76-0.91 (m, 2H), 1.08-1.37 (m, 5H), 1.53-1.67 (m, 6H), 1.72-1.93 (m, 2H), 1.95-2.20 (m, 3H), 2.16 (s, 3H), 2.36 (t, J=7.2 Hz, 2H), 2.42-2.56 (m, 2H), 2.83 (s, 3H), 3.52 (s, 2H), 3.64-3.77 (m, 1H), 6.98 (d, J=6 Hz, 1H), 7.04-7.28 (m, 5H), 7.34 (d, J=8.1 Hz, 1H), 7.54 (d, J=8.1 Hz, 1H).

MS (ESI(-)) m/e 527 (M-H); Analysis calc'd for C₂₉H₃₉LiN₂O₅S•0.15H₂O•0.40HoAc: C, 60.32; H, 6.82; N, 4.74; found: C, 60.25; H, 6.97; N, 4.92.



Example 1060

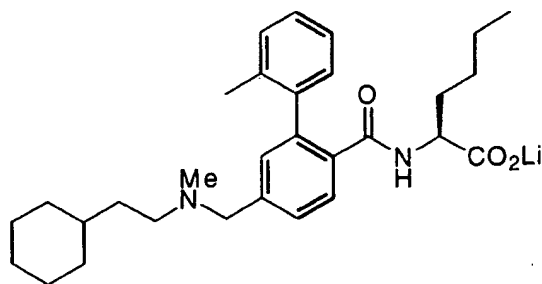
N-[4-(N-(2-Cyclohexylethyl)-N-methylaminomethyl)-2-(2-methylphenyl)benzoyl]norleucine, lithium salt



Example 1060A

N-[4-(N-(2-Cyclohexylethyl)-N-methylaminomethyl)-2-(2-methylphenyl)benzoyl]norleucine, Methyl Ester

The title compound was prepared according to example 608D, substituting L-norleucine methyl ester•HCl for L-methionine methyl ester•HCl. MS(APCI(+)) 493 (M+H)⁺. MS(APCI(-)) 491 (M-H)⁻.

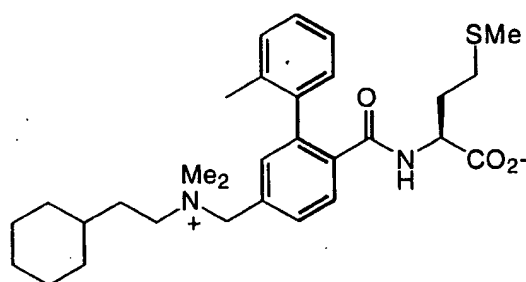
**Example 1060B**

N-[4-(N-(2-Cyclohexylethyl)-N-methylaminomethyl)-2-(2-methylphenyl)benzoyl]norleucine, lithium salt

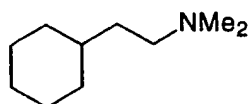
N-[4-(N-(2-Cyclohexylethyl)-N-methylaminomethyl)-2-(2-methylphenyl)benzoyl]norleucine methyl ester was converted into the title compound according to the procedure in example 608E, and was isolated as a white powder.

¹H NMR (300 MHz, DMSO) δ 0.62-0.90 (m, 7H), 0.97-1.44 (m, 10H), 1.52-1.64 (m, 5H), 1.95-2.18 (m, 3H), 2.13 (s, 3H), 2.33 (t, J=6 Hz, 2H), 3.48 (s, 2H), 3.56-3.66 (m, 1H), 6.80-6.89 (m, 1H), 7.01-7.22 (m, 5H), 7.30 (d, J=7.8 Hz, 1H), 7.46 (d, J=7.8 Hz, 1H).

MS (ESI(-)) m/e 477 (M-H); Analysis calc'd for C₃₀H₄₁LiN₂O₃•0.9H₂O: C, 71.95; H, 8.61; N, 5.59; found: C, 72.00; H, 8.36; N, 5.50.

**Example 1061**

N-[4-(N-(2-Cyclohexylethyl)-N,N-dimethylaminomethyl)-2-(2-methylphenyl)benzoyl]methionine, Internal salt

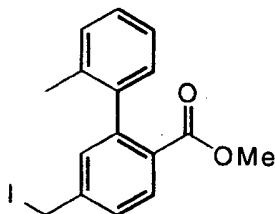
**Example 1061A**

N,N-Dimethyl-2-cyclohexylethylamine

The title compound was prepared from N-methylcyclohexylethylamine (example 608A) according to the procedure described in example 1056A.

¹H NMR (300 MHz, CDCl₃) δ 0.80-0.95 (m, 2H), 1.10-1.39 (m, 6H), 1.60-1.74 (m, 5H), 2.20 (s, 6H), 2.23-2.28 (m, 2H).

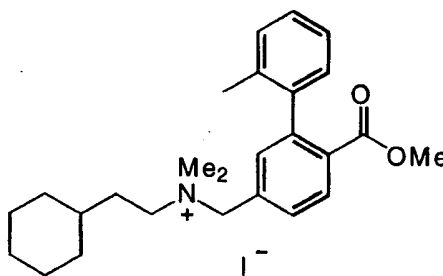
MS (DCI/NH₃) m/e 156 (M+H)⁺.



Example 1061B

4-Iodomethyl-2-(2-methylphenyl)benzoic acid, methyl ester

Triphenylphosphine (5.16g), and imidazole (1.34g) were dissolved in 3:1 ether:acetonitrile (80mL), and the reaction was cooled to 0°C. Iodine (5.0g) was added with vigorous stirring, and the reaction was warmed to ambient temperature. After 1h, the reaction was recooled to 0°C and 4-hydroxymethyl-2-(2-methylphenyl)benzoic acid, methyl ester (example 1178C, 4.6g) was added as a solution in ether (20mL). After 4h at ambient temperature, the reaction was diluted with hexane/ether (1:1, 200mL) and filtered. The filtrate was washed with a dilute solution of Na₂SO₃ until colorless, then with water (2X50mL). The organic extracts were washed with brine (20mL), dried (MgSO₄), filtered and concentrated. The residue was purified by silica gel chromatography eluting with 10% EtOAc/hexane to give a light yellow oil (4.7g) which slowly crystallizes in the freezer. ¹H NMR (300MHz, CDCl₃) δ 2.06 (s, 3H), 3.60 (s, 3H), 4.45 (AB_q, J_{AB}=9.7Hz, Δν_{AB}=6.7Hz, 2H), 7.03 (brd, J=6.6Hz, 1H), 7.17-7.29 (m, 4H), 7.41 (dd, J=8.1, 1.6Hz, 1H), 7.90 (d, J=8.1Hz, 1H)). MS(CI/NH₃) m/e: (M+NH₄)⁺ 384.

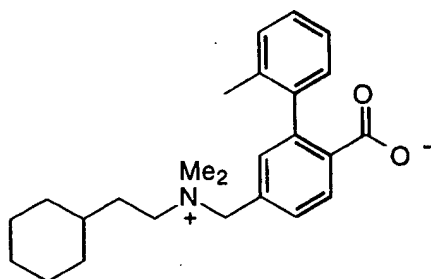


Example 1061C

4-(N-(2-Cyclohexylethyl)-N,N-dimethylaminomethyl)-2-(2-methylphenyl)benzoic acid, Methyl Ester, Iodide

To a solution of 4-iodomethyl-2-(2-methylphenyl)benzoic acid methyl ester (0.5g) in
 10845 dichloromethane (1mL) was added N,N-dimethyl-2-cyclohexylethylamine (0.233mg), and
 the reaction was stirred at ambient temperature for 2h. The reaction was concentrated to give
 a light yellow foam (760mg, 100%).

¹H NMR (300 MHz, CDCl₃) δ 0.89-1.44 (m, 6H), 1.60-1.73 (m, 7H), 2.06 (s, 3H), 3.34
 (s, 6H), 3.55-3.63 (m, 2H), 3.64 (s, 3H), 5.14 (ABq, Δν_{AB}=56 Hz, J_{AB}=12.7 Hz, 2H),
 10850 7.01 (d, J=7.5 Hz, 1H), 7.17-7.32 (m, 3H), 7.39 (d, J=1.8 Hz, 1H), 7.88 (dd, J=8.1, 1.8
 Hz, 1H), 8.02 (d, J=8.1 Hz, 1H).



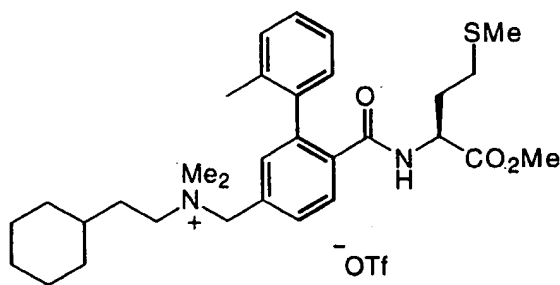
Example 1061D

10855 4-(N-(2-Cyclohexylethyl)-N,N-dimethylaminomethyl)-2-(2-methylphenyl)benzoate, Internal salt

To a solution of 4-(N-(2-cyclohexylethyl)-N,N-dimethylaminomethyl)-2-(2-
 methylphenyl)benzoic acid methyl ester, iodide (700mg) in methanol (3mL) was added 5M
 LiOH (0.54mL). The reaction was refluxed for 1h, then stirred at ambient temperature
 10860 overnight. The reaction was diluted with water (30mL), and purified by preparative reverse-
 phase medium pressure chromatography, eluting with a gradient of methanol/water/TFA
 (0.1%) to give a tan syrup (711mg).

¹H NMR (300 MHz, DMSO) δ 0.90-1.03 (m, 2H), 1.10-1.28 (m, 5H), 1.57-1.73 (m, 6H),
 2.06 (s, 3H), 2.97 (s, 6H), 3.24-3.35 (m, 2H), 4.53-4.57 (m, 2H), 7.07 (d, J=6.9 Hz,
 10865 1H), 7.18-7.30 (m, 3H), 7.43 (d, J=1.5 Hz, 1H), 7.64 (dd, J=8.1, 1.5 Hz, 1H), 7.96 (d,
 J=8.1 Hz, 1H).

MS (ESI) m/e 380 (M+H)⁺.



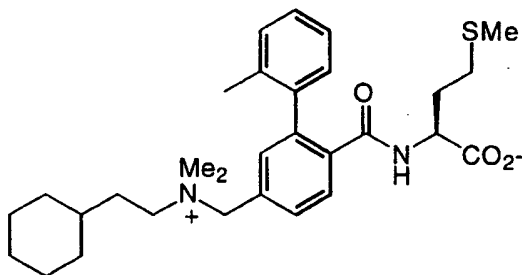
10870

Example 1061EN-[4-(N-(2-Cyclohexylethyl)-N,N-dimethylaminomethyl)-2-(2-methylphenyl)benzoyl]methionine, Methyl Ester, Triflate

To a solution of 4-(N-(2-cyclohexylethyl)-N,N-dimethylaminomethyl)-2-(2-methylphenyl)benzoate internal salt (771mg) in dichloromethane (5mL) at ambient temperature was added oxalyl chloride (5mL of a 2M solution in CH₂Cl₂). As gas evolution slowed, DMF (5 drops) was added. After stirring at ambient temperature for 20min, the reaction was warmed to reflux for 2h, then cooled, and the solvent was removed under a stream of dry nitrogen to give a tan solid. To a solution of the acid chloride dissolved in dry dichloromethane (10mL) at 0°C was added triethylamine (0.47mL), and L-methionine methyl ester·HCl (320mg). After stirring at ambient temperature overnight, the reaction was concentrated, dissolved in 1:1 methanol/water (30mL), and purified by preparative reverse-phase medium pressure chromatography, eluting with a gradient of methanol/water/TFA (0.1%) to give a tan foam (330mg).

¹H NMR (300 MHz, CDCl₃) δ 0.88-1.40 (m, 7H), 1.60-1.76 (m, 6H), 1.82-1.95 (m, 2H), 2.00-2.19 (m, 8H), 3.21 (brs, 6H), 3.29-3.37 (m, 2H), 3.68 (s, 3H), 4.58-4.65 (m, 3H), 6.09 (d, J=6 Hz, 1H), 7.13-7.40 (m, 6H), 7.57 (brd, J=7.8 Hz, 1H), 8.00 ("t", J=7.8 Hz, 1H).

MS (ESI(-)) m/e 637 (M-H)⁻, 751 (M+TFA-H)⁻.



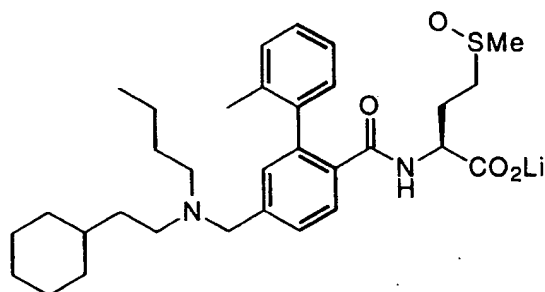
10890

Example 1061FN-[4-(N-(2-Cyclohexylethyl)-N,N-dimethylaminomethyl)-2-(2-methylphenyl)benzoyl]methionine, Internal salt

N-[4-(N-(2-Cyclohexylethyl)-N,N-dimethylaminomethyl)-2-(2-methylphenyl)benzoyl]methionine methyl ester triflate (330mg) was dissolved in methanol (2mL), and 5M LiOH (0.21mL, 2equiv) was added. After stirring at ambient temperature overnight, the reaction was diluted with water (10mL), and purified by preparative reverse-phase medium pressure chromatography, eluting with a gradient of methanol/water/TFA (0.1%) to give a tan powder (168mg) after lyophilization from acetonitrile-water.

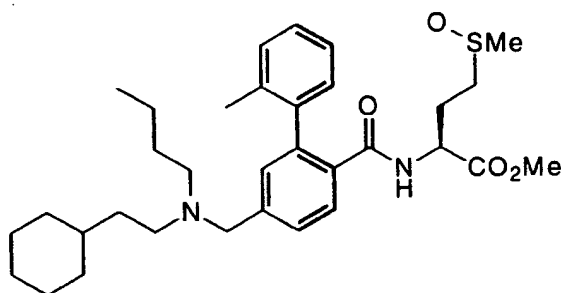
10895

- 10900 ^1H NMR (300 MHz, DMSO) δ 0.87-1.04 (m, 2H), 1.08-1.33 (m, 4H), 1.59-1.92 (m, 10H), 1.96 (s, 3H), 2.00-2.24 (m, 4H), 2.97 (brs, 6H), 3.24-3.35 (m, 2H), 4.20-4.30 (m, 1H), 4.56 (brs, 2H), 7.13-7.27 (m, 5H), 7.43 (brs, 1H), 7.62 (brs, 2H), 8.30 (brd, $J=5$ Hz, 1H).
 MS (ESI(+)) m/e 511 (M+H); Analysis calc'd for $\text{C}_{30}\text{H}_{42}\text{N}_2\text{O}_3\text{S}\cdot 0.65\text{H}_2\text{O}\cdot 1.30\text{TFA}$: C, 58.38; H, 6.70; N, 4.18; found: C, 58.35; H, 6.67; N, 4.26.



Example 1062

- 10910 (2S) 2-N-[4-(N-(2-Cyclohexylethyl)-N-butylaminomethyl)-2-(2-methylphenyl)benzoyl]amino-4-methylsulfenylbutanoate, lithium salt

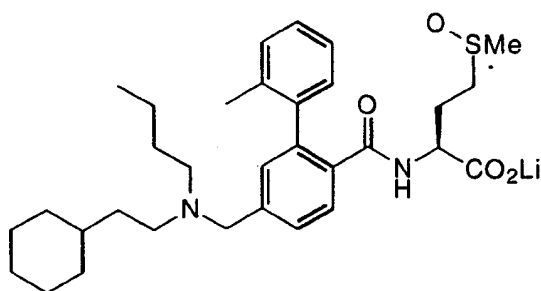


Example 1062A

- 10915 (2S) 2-N-[4-(N-(2-Cyclohexylethyl)-N-butylaminomethyl)-2-(2-methylphenyl)benzoyl]amino-4-methylsulfenylbutanoate, Methyl Ester

To a solution of N-[4-(N-(2-cyclohexylethyl)-N-butylaminomethyl)-2-(2-methylphenyl)benzoyl]methionine methyl ester (example 1178I, 90mg) in dichloromethane (1mL) at 0°C was added trifluoroacetic acid (0.023mL), then 30% hydrogen peroxide (0.05mL). After 2h, the reaction was quenched by addition of sodium sulfite (100mg). The reaction was filtered, concentrated, and the residue was purified by silica gel chromatography eluting with 2.5%-5.0% methanol/dichloromethane to give the title compound as a colorless oil (75mg, 79%). MS(APCI(+)) 569 (M+H)⁺. MS(APCI(-)) 603 (M+Cl)⁻.

- 10920



10925

Example 1062B

(2S) 2-N-[4-(N-(2-Cyclohexylethyl)-N-butylaminomethyl)-2-(2-methylphenyl)benzoyl]amino-4-methylsulfenylbutanoate, lithium salt

10930

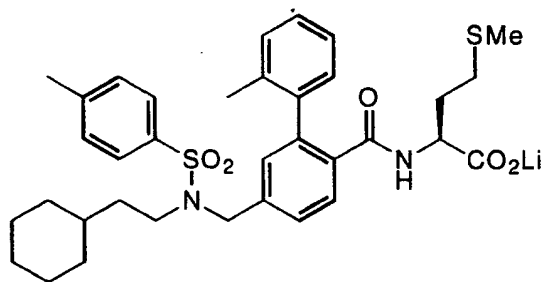
(2S) 2-N-[4-(N-(2-Cyclohexylethyl)-N-butylaminomethyl)-2-(2-methylphenyl)benzoyl]amino-4-methylsulfenylbutanoate methyl ester was converted to the title compound according to the procedure in example 608E, with the exception that the product was isolated as a colorless foam after trituration with dichloromethane and removal of the solvent under reduced pressure.

10935

¹H NMR (300 MHz, DMSO) δ 0.76-0.87 (m, 5H), 1.02-1.44 (m, 9H), 1.52-1.88 (m, 8H), 1.92-2.24 (m, 6H), 2.33-2.43 (m, 6H), 3.54 (brs, 2H), 3.64-3.75 (m, 1H), 6.97 (brd, J=5.1 Hz, 1H), 7.06-7.25 (m, 5H), 7.32 (brd, J=7.5 Hz, 1H), 7.49 (d, J=7.5 Hz, 0.5H), 7.51 (d, J=7.5 Hz, 0.5H).

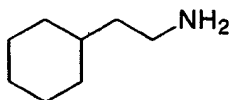
MS (ESI(-)) m/e 553 (M-H).

10940

Example 1063

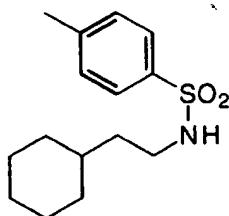
N-[4-(N-(2-Cyclohexylethyl)-N-p-toluenesulfonylaminomethyl)-2-(2-methylphenyl)benzoyl]methionine, lithium salt

10945

Example 1063A

2-Cyclohexylethylamine

Phenethylamine (50g) was dissolved in 1000mL of glacial acetic acid in a pressure vessel, followed by addition of platinum oxide (15g). After shaking under 4atm of hydrogen for 48h, the reaction was filtered and the acetic acid was removed under reduced pressure. The residue was taken up in water (1000mL), basified with 5N NaOH, and washed with ether (5X250mL). The ether extracts were washed with brine (250mL), dried (MgSO₄), filtered and concentrated to afford a light yellow oil which was purified by fractional distillation at atmospheric pressure (bp 185°C, 49.5g, 94%).
¹H NMR(CDCl₃, 300MHz) δ 0.83-0.95 (m, 2H), 1.00-1.38 (m, 8H), 1.60-1.73 (m, 5H), 2.71 (dd, J=8.1, 7.2Hz, 2H).



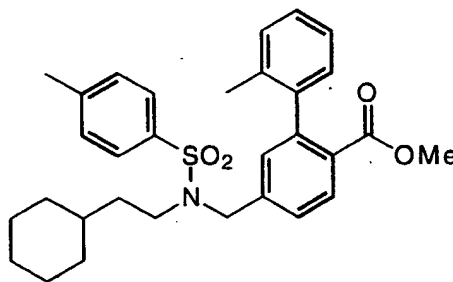
Example 1063B

N-2-Cyclohexylethyl-p-toluenesulfonamide

To a solution of p-toluenesulfonyl chloride (210mg), and diisopropylethylamine (0.35mL) in dichloroethane (3mL) was added 2-cyclohexylethylamine (0.15mL, 1.0mmol). After 6h, the reaction was diluted with 1:1 EtOAc/hexane (25mL), washed with water (5mL), 1M HCl (2X5mL) and brine (5mL). The organic solution was dried (MgSO₄), filtered and concentrated to afford a colorless crystalline solid (300mg).

¹H NMR (300 MHz, CDCl₃) δ 0.75-0.91 (m, 2H), 1.06-1.27 (m, 4H), 1.33 (q, J=6.9 Hz, 2H), 1.59-1.70 (m, 5H), 2.43 (s, 3H), 2.95 (q, J=6.9 Hz, 2H), 4.21 (brt, J=5.9 Hz, 1H), 7.31 (d, J=7.8 Hz, 2H), 7.74 (d, J=8.4 Hz, 2H).

MS (DCI/NH₃) m/e 299 (M+NH₄)⁺.

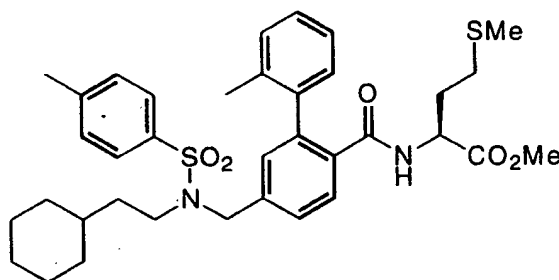


Example 1063C

4-(N-(2-Cyclohexylethyl)-N-p-toluenesulfonylaminomethyl)-2-(2-methylphenyl)benzoic acid, Methyl Ester

To a solution of N-2-Cyclohexylethyl-p-toluenesulfonamide (300mg) in DMF (5mL) was added NaH (56mg of a 60% dispersion in mineral oil). After gas evolution subsided, 4-bromomethyl-2-(2-methylphenyl)benzoic acid methyl ester (example 1178D, 266mg) was added. After stirring at ambient temperature for 1.5h, the reaction was quenched by addition of water (10mL), and diluted with 50% EtOAc/hexane (50mL). The organic solution was washed with water (10mL), brine (2X10mL), dried (MgSO₄), filtered and concentrated. The residue was purified by silica gel chromatography eluting with 10% EtOAc/hexane to give the title compound as a colorless oil (250mg, 70%).

¹H NMR (300 MHz, CDCl₃) δ 0.64-0.81 (m, 2H), 1.00-1.15 (m, 4H), 1.16-1.27 (m, 2H), 1.42-1.64 (m, 5H), 2.03 (s, 3H), 2.41 (s, 3H), 3.12 (dd, J=9.3, 7.5 Hz, 2H), 3.61 (s, 3H), 4.35 (s, 2H), 7.00 (brd, J=7.2 Hz, 1H), 7.08 (d, J=1.5 Hz, 1H), 7.16-7.27 (m, 3H), 7.28 (d, J=8.1 Hz, 2H), 7.37 (dd, J=8.1, 1.5 Hz, 1H), 7.71 (d, J=8.4 Hz, 2H), 7.42 (d, J=7.1 Hz, 1H).

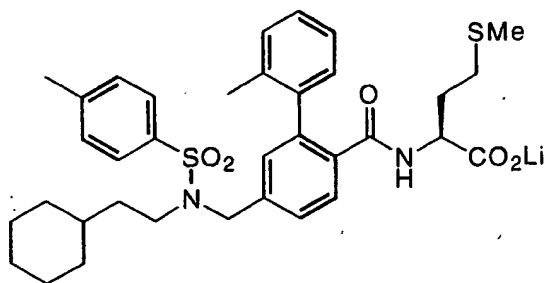


Example 1063D

N-[4-(N-(2-Cyclohexylethyl)-N-p-toluenesulfonylaminomethyl)-2-(2-methylphenyl)benzoyl]methionine, Methyl Ester

4-(N-(2-Cyclohexylethyl)-N-p-toluenesulfonylaminomethyl)-2-(2-methylphenyl)benzoic acid methyl ester was converted into the title compound according to the procedures described in examples 608C and D to afford a colorless oil.

¹H NMR (300 MHz, CDCl₃) δ 0.68-0.82 (m, 2H), 1.00-1.28 (m, 4H), 1.43-1.66 (m, 7H), 1.78-1.92 (m, 2H), 1.98-2.17 (m, 8H), 2.41 (s, 3H), 3.13 (t, J=7.8 Hz, 2H), 3.66 (s, 3H), 4.36 (s, 2H), 4.55-4.67 (m, 1H), 5.88 (brd, J=7.5 Hz, 1H), 7.08-7.37 (m, 8H), 7.71 (d, J=8.4 Hz, 2H), 7.90 ("dd", J=15, 8.4 Hz, 1H). MS(APCI(+)) 651 (M+H)⁺. MS(APCI(-)) 649 (M-H)⁻.

Example 1063E

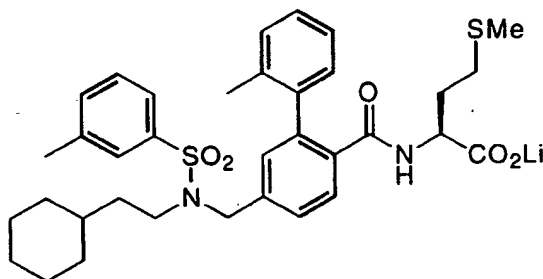
11005 N-[4-(N-(2-Cyclohexylethyl)-N-p-toluenesulfonylaminomethyl)-2-(2-
methylphenyl)benzoyl]methionine, lithium salt

N-[4-(N-(2-Cyclohexylethyl)-N-p-toluenesulfonylaminomethyl)-2-(2-methylphenyl)benzoyl]methionine methyl ester was converted to the title compound according to the procedure described in example 608E, and was isolated as a white powder.

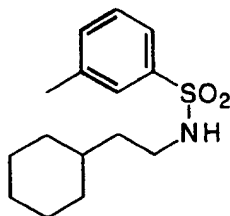
11010 ¹H NMR (300 MHz, DMSO) δ 0.60-0.78 (m, 2H), 0.98-1.20 (m, 6H), 1.38-1.60 (m, 6H), 1.70-1.95 (m, 4H), 1.81 (s, 3H), 1.96-2.18 (m, 3H), 3.03-3.12 (m, 2H), 3.60-3.73 (m, 1H), 4.35 (s, 2H), 6.95 (d, J=6.3 Hz, 1H), 7.0-7.27 (m, 5H), 7.35 (d, J=7.5 Hz, 1H), 7.40 (d, J=8.1 Hz, 2H), 7.50 (d, J=7.8 Hz, 1H), 7.73 (s, J=6.6 Hz, 2H).

MS (APCI(-)) m/e 635 (M-H); Analysis calc'd for C₃₅H₄₃LiN₂O₅S₂•0.80H₂O: C, 63.96;

11015 H, 6.84; N, 4.26; found: C, 63.98; H, 6.68; N, 4.09.

Example 1064

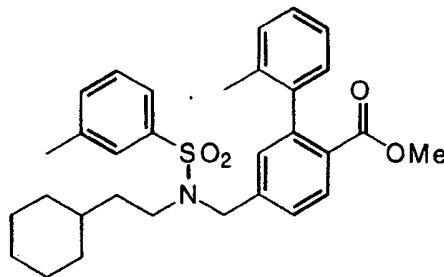
11020 N-[4-(N-(2-Cyclohexylethyl)-N-m-toluenesulfonylaminomethyl)-2-(2-
methylphenyl)benzoyl]methionine, lithium salt

Example 1064A

11025

N-2-Cyclohexylethyl-m-toluenesulfonamide

The title compound was prepared according to example 1063B, replacing p-toluenesulfonyl chloride with m-toluenesulfonyl chloride to afford a colorless oil. MS (DCI/NH₃) m/e 299 (M+NH₄)⁺.

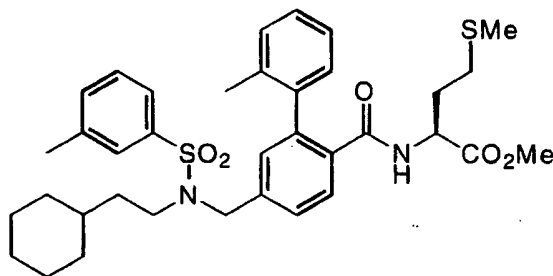


11030

Example 1064B

4-(N-(2-Cyclohexylethyl)-N-m-toluenesulfonylaminomethyl)-2-(2-methylphenyl)benzoic acid, Methyl Ester

N-2-Cyclohexylethyl-m-toluenesulfonamide was converted into the title compound according to the procedure in example 1063C to afford a colorless oil. MS (DCI/NH₃) m/e 537 (M+NH₄)⁺.

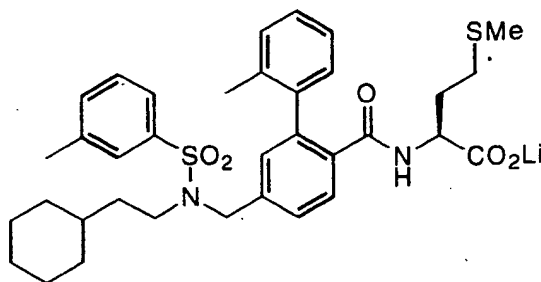
Example 1064C

11040

N-[4-(N-(2-Cyclohexylethyl)-N-m-toluenesulfonylaminomethyl)-2-(2-methylphenyl)benzoyl]methionine, Methyl Ester

4-(N-(2-Cyclohexylethyl)-N-m-toluenesulfonylaminomethyl)-2-(2-methylphenyl)benzoic acid methyl ester was converted into the title compound according to the procedures described in examples 608C and D to afford a colorless oil. MS(APCI(+)) 651 (M+H)⁺. MS(APCI(-)) 649 (M-H)⁻.

11045

**Example 1064D**

N-[4-(N-(2-Cyclohexylethyl)-N-m-toluenesulfonylaminomethyl)-2-(2-methylphenyl)benzoyl]methionine, lithium salt

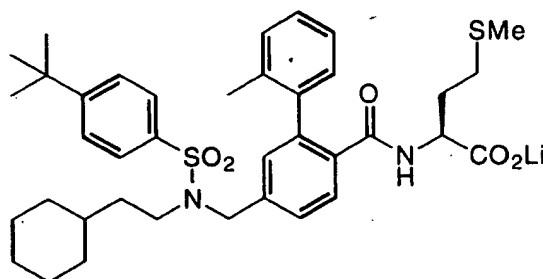
11050

N-[4-(N-(2-Cyclohexylethyl)-N-m-toluenesulfonylaminomethyl)-2-(2-methylphenyl)benzoyl]methionine methyl ester was converted to the title compound according to the procedure described in example 608E, and was isolated as a white powder.
¹H NMR (300 MHz, DMSO) δ 0.60-0.77 (m, 2H), 1.00-1.20 (m, 6H), 1.40-1.89 (m, 10H), 1.93 (s, 3H), 1.95-2.14 (m, 3H), 2.39 (s, 3H), 3.05-3.15 (m, 2H), 3.60-3.72 (m, 1H), 4.38 (s, 2H), 6.94 (d, J=5.7 Hz, 1H), 7.02-7.27 (m, 5H), 7.36 (d, J=8.1 Hz, 1H), 7.44-7.54 (m, 3H), 7.60-7.69 (m, 2H).

11055

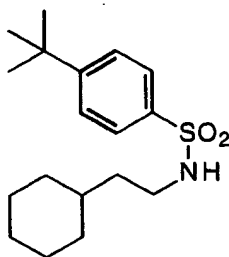
MS (ESI(-)) m/e 635 (M-H); Analysis calc'd for C₃₅H₄₃LiN₂O₅S₂•1.30H₂O: C, 63.10; H, 6.90; N, 4.20; found: C, 63.06; H, 6.53; N, 4.18.

11060

**Example 1065**

N-[4-(N-(2-Cyclohexylethyl)-N-p-tert-butylbenzenesulfonylaminomethyl)-2-(2-methylphenyl)benzoyl]methionine, lithium salt

11065

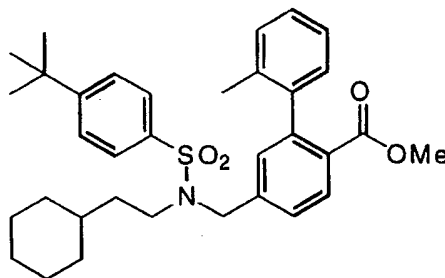


Example 1065AN-2-Cyclohexylethyl-p-tert-butylbenzenesulfonamide

11070

The title compound was prepared according to example 1063B, replacing p-toluenesulfonyl chloride with p-tert-butylbenzenesulfonyl chloride to afford a white crystalline solid.

MS (DCI/NH₃) m/e 341 (M+NH₄)⁺.



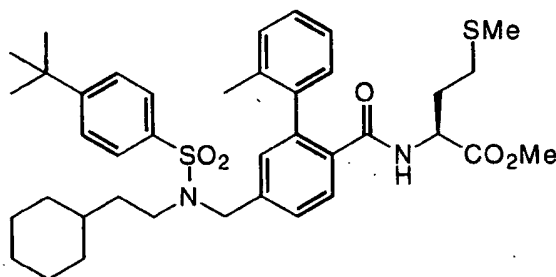
11075

Example 1065B

4-(N-(2-Cyclohexylethyl)-N-p-tert-butylbenzenesulfonylaminomethyl)-2-(2-methylphenyl)benzoic acid, Methyl Ester

11080

N-2-Cyclohexylethyl-p-tert-butylbenzenesulfonamide (300mg) was converted into the title compound according to the procedure in example 1063C to afford a colorless oil.
MS (DCI/NH₃) m/e 579 (M+NH₄)⁺.

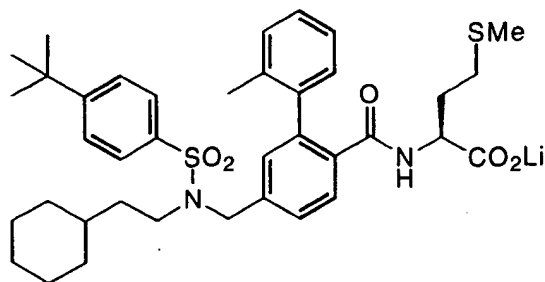
Example 1065C

11085

N-[4-(N-(2-Cyclohexylethyl)-N-p-tert-butylbenzenesulfonylaminomethyl)-2-(2-methylphenyl)benzoyl]methionine, Methyl Ester

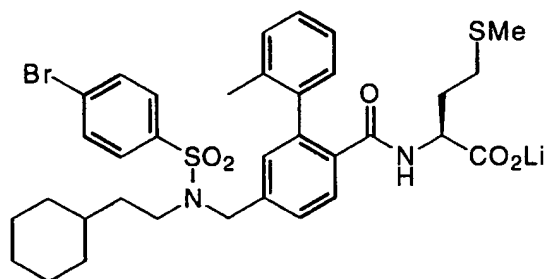
11090

4-(N-(2-Cyclohexylethyl)-N-p-tert-butylbenzenesulfonylaminomethyl)-2-(2-methylphenyl)benzoic acid methyl ester was converted into the title compound according to the procedures described in examples 608C and D to afford a colorless oil. MS(ESI(+)) 693 (M+H)⁺. MS(ESI(-)) 691 (M-H)⁻.

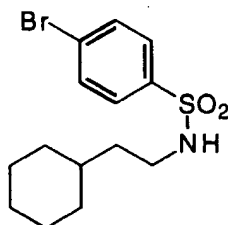
Example 1065D

N-[4-(N-(2-Cyclohexylethyl)-N-p-tert-butylbenzenesulfonylaminomethyl)-2-(2-methylphenyl)benzoyl]methionine, lithium salt

N-[4-(N-(2-Cyclohexylethyl)-N-p-tert-butylbenzenesulfonylaminomethyl)-2-(2-methylphenyl)benzoyl]methionine methyl ester was converted to the title compound according to the procedure described in example 608E, and was isolated as a white powder. ¹H NMR (300 MHz, DMSO) δ 0.60-0.75 (m, 2H), 0.96-1.20 (m, 6H), 1.33 (s, 9H), 1.38-1.88 (m, 10H), 1.93 (s, 3H), 1.95-2.18 (m, 3H), 3.04-3.13 (m, 2H), 3.59-3.70 (m, 1H), 4.37 (s, 2H), 6.95 (d, J=5.7 Hz, 1H), 7.10-7.28 (m, 5H), 7.35 (d, J=7.8 Hz, 1H), 7.50 (d, J=6.3 Hz, 1H), 7.63 (d, J=8.4 Hz, 2H), 7.78 (d, J=7.5 Hz, 2H). MS (ESI(-)) m/e 677 (M-H); Analysis calc'd for C₃₈H₄₉LiN₂O₅S₂•1.55H₂O: C, 64.03; H, 7.37; N, 3.93; found: C, 63.98; H, 7.15; N, 3.92.

Example 1066

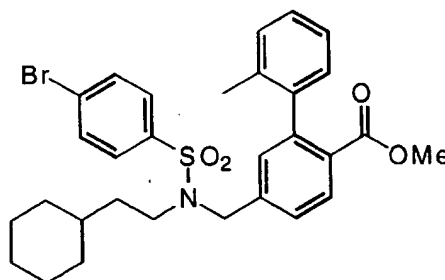
N-[4-(N-(2-Cyclohexylethyl)-N-p-bromobenzenesulfonylaminomethyl)-2-(2-methylphenyl)benzoyl]methionine, lithium salt

Example 1066A

N-2-Cyclohexylethyl-p-bromobenzenesulfonamide

11115 The title compound was prepared according to example 1063B, replacing p-toluenesulfonyl chloride with p-bromobenzenesulfonyl chloride to afford a white crystalline solid.

MS (DCI/NH₃) m/e 363 (M(⁷⁹Br)+NH₄)⁺, 365 (M(⁸¹Br)+NH₄)⁺.



11120

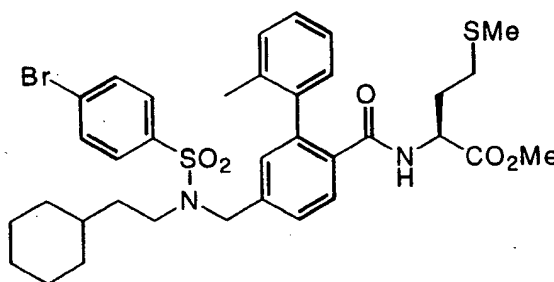
Example 1066B

4-(N-(2-Cyclohexylethyl)-N-p-bromobenzenesulfonylaminomethyl)-2-(2-methylphenyl)benzoic acid, Methyl Ester

N-2-Cyclohexylethyl-p-bromobenzenesulfonamide (300mg) was converted into the

11125 title compound according to the procedure in example 1063C to afford a colorless oil.

MS (DCI/NH₃) m/e 601 (M(⁷⁹Br)+NH₄)⁺, 603 (M(⁸¹Br)+NH₄)⁺.

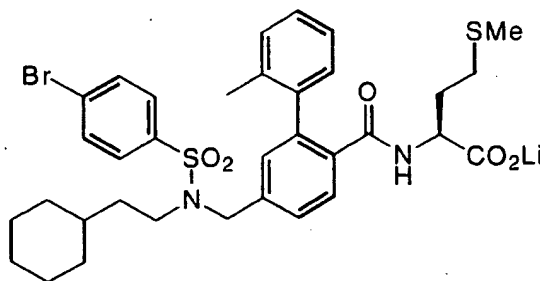
Example 1066C

11130

N-[4-(N-(2-Cyclohexylethyl)-N-p-bromobenzenesulfonylaminomethyl)-2-(2-methylphenyl)benzoyl]methionine, Methyl Ester

4-(N-(2-Cyclohexylethyl)-N-p-bromobenzenesulfonylaminomethyl)-2-(2-methylphenyl)benzoic acid methyl ester was converted into the title compound according to the procedures described in examples 608C and D to afford a colorless oil. MS(APCI(+))

11135 715 (M(⁷⁹Br)+H)⁺, 717 (M(⁸¹Br)+H)⁺. MS(APCI(-)) 749 (M(⁷⁹Br)+Cl)⁻, 751 (M(⁸¹Br)+Cl)⁻.

Example 1066D

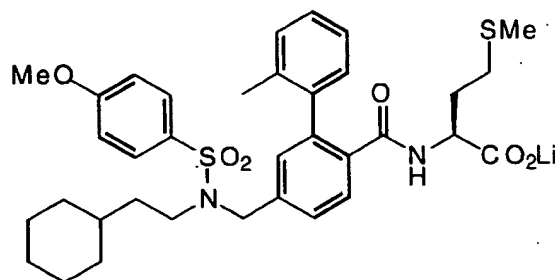
11140 N-[4-(N-(2-Cyclohexylethyl)-N-p-bromobenzenesulfonylaminomethyl)-2-(2-methylphenyl)benzoyl]methionine, lithium salt

N-[4-(N-(2-Cyclohexylethyl)-N-p-bromobenzenesulfonylaminomethyl)-2-(2-methylphenyl)benzoyl]methionine methyl ester was converted to the title compound according to the procedure described in example 608E, and was isolated as a white powder.

11145 ^1H NMR (300 MHz, DMSO) δ 0.60-0.75 (m, 2H), 0.94-1.21 (m, 6H), 1.38-1.88 (m, 10H), 1.93 (s, 3H), 1.95-2.15 (m, 3H), 3.06-3.15 (m, 2H), 3.55-3.67 (m, 1H), 4.36 (s, 2H), 6.96 (d, $J=6$ Hz, 1H), 7.03-7.26 (m, 5H), 7.37 (d, $J=8.1$ Hz, 1H), 7.54 (d, $J=8.1$ Hz, 1H), 7.76-7.85 (m, 4H).

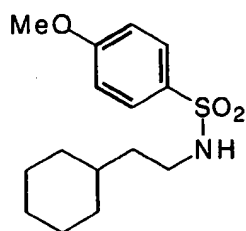
MS (ESI(-)) m/e 699 ($M(^{79}\text{Br})+H$) $^+$, 701 ($M(^{81}\text{Br})+H$) $^+$; Analysis calc'd for

11150 $\text{C}_{34}\text{H}_{40}\text{BrLiN}_2\text{O}_5\text{S}_2 \cdot 0.95\text{H}_2\text{O}$: C, 56.34; H, 5.83; N, 3.86; found: C, 56.33; H, 5.66; N, 3.48.

Example 1067

11155

N-[4-(N-(2-Cyclohexylethyl)-N-p-methoxybenzenesulfonylaminomethyl)-2-(2-methylphenyl)benzoyl]methionine, lithium salt

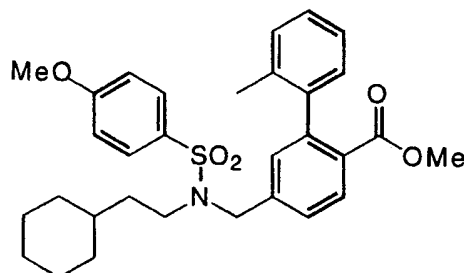


11160

Example 1067AN-2-Cyclohexylethyl-p-methoxybenzenesulfonamide

The title compound was prepared according to example 1063B, replacing p-toluenesulfonyl chloride with p-methoxybenzenesulfonyl chloride to afford a colorless oil. MS (DCI/NH₃) m/e 315 (M+NH₄)⁺.

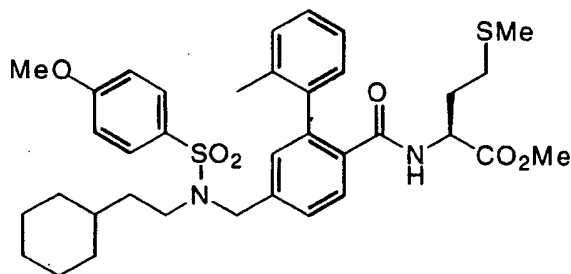
11165

Example 1067B

4-(N-(2-Cyclohexylethyl)-N-p-methoxybenzenesulfonylaminomethyl)-2-(2-methylphenyl)benzoic acid, Methyl Ester

11170

N-2-Cyclohexylethyl-p-methoxybenzenesulfonamide (300mg) was converted into the title compound according to the procedure in example 1063C to afford a colorless oil. MS (DCI/NH₃) m/e 553 (M+NH₄)⁺.



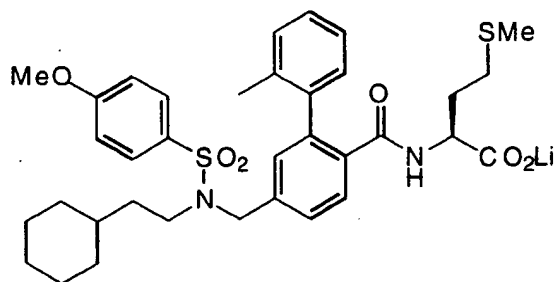
11175

Example 1067C

N-[4-(N-(2-Cyclohexylethyl)-N-p-methoxybenzenesulfonylaminomethyl)-2-(2-methylphenyl)benzoyl]methionine, Methyl Ester

4-(N-(2-Cyclohexylethyl)-N-p-methoxybenzenesulfonylaminomethyl)-2-(2-methylphenyl)benzoic acid methyl ester was converted into the title compound according to the procedures described in examples 608C and D to afford a colorless oil. MS(APCI(+)) 667 (M+H)⁺. MS(APCI(-)) 701 (M+Cl)⁻.

11180

Example 1067D

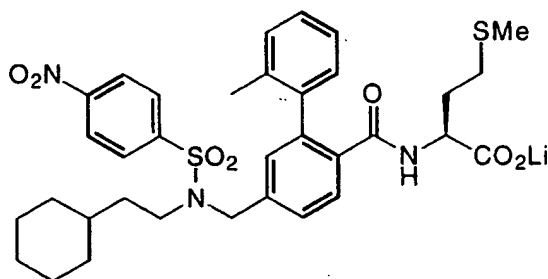
11185 N-[4-(N-(2-Cyclohexylethyl)-N-p-methoxybenzenesulfonylaminomethyl)-2-(2-methylphenyl)benzoyl]methionine, lithium salt

N-[4-(N-(2-Cyclohexylethyl)-N-p-methoxybenzenesulfonylaminomethyl)-2-(2-methylphenyl)benzoyl]methionine methyl ester was converted to the title compound according to the procedure described in example 608E, and was isolated as a white powder.

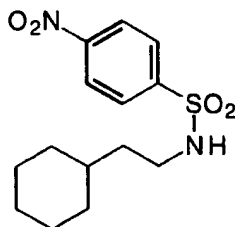
11190 ^1H NMR (300 MHz, DMSO) δ 0.62-0.78 (m, 2H), 1.00-1.22 (m, 6H), 1.37-1.85 (m, 10H), 1.90 (s, 3H), 1.90-2.16 (m, 3H), 3.01-3.10 (m, 2H), 3.58-3.67 (m, 1H), 3.83 (s, 3H), 4.32 (s, 2H), 6.94 (d, $J=6$ Hz, 1H), 7.04-7.26 (m, 5H), 7.11 (d, $J=8.7$ Hz, 2H), 7.35 (dd, $J=8.1$, 1 Hz, 1H), 7.51 (d, $J=8.1$ Hz, 1H), 7.77 (d, $J=8.7$ Hz, 2H).

MS (APCI(-)) m/e 651 (M-H); Analysis calc'd for $\text{C}_{35}\text{H}_{43}\text{LiN}_2\text{O}_6\text{S}_2 \cdot 1.85\text{H}_2\text{O}$: C, 61.35;

11195 H, 6.87; N, 4.09; found: C, 61.36; H, 6.48; N, 3.91.

Example 1068

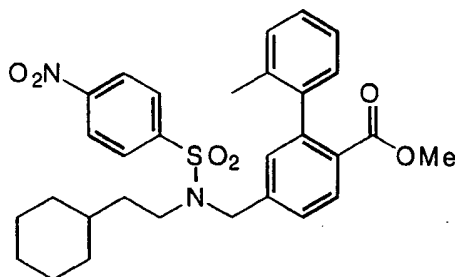
11200 N-[4-(N-(2-Cyclohexylethyl)-N-p-nitrobenzenesulfonylaminomethyl)-2-(2-methylphenyl)benzoyl]methionine, lithium salt

Example 1068A

11205

N-2-Cyclohexylethyl-p-nitrobenzenesulfonamide

The title compound was prepared according to example 1063B, replacing p-toluenesulfonyl chloride with p-nitrobenzenesulfonyl chloride to afford a colorless oil. MS (DCI/NH₃) m/e 330 (M+NH₄)⁺.

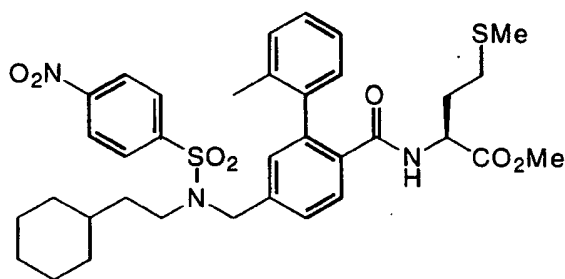


11210

Example 1068B

4-(N-(2-Cyclohexylethyl)-N-p-nitrobenzenesulfonylaminomethyl)-2-(2-methylphenyl)benzoic acid, Methyl Ester

N-2-Cyclohexylethyl-p-nitrobenzenesulfonamide (300mg) was converted into the title compound according to the procedure in example 1063C to afford a colorless oil. MS (DCI/NH₃) m/e 568 (M+NH₄)⁺.

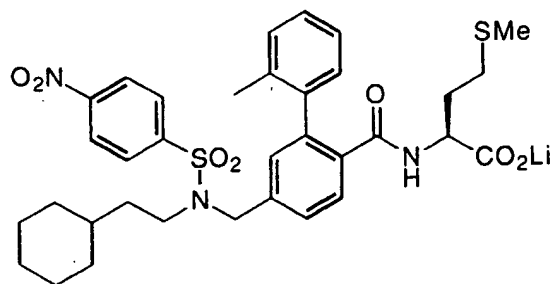
Example 1068C

11220

N-[4-(N-(2-Cyclohexylethyl)-N-p-nitrobenzenesulfonylaminomethyl)-2-(2-methylphenyl)benzoyl]methionine, Methyl Ester

4-(N-(2-Cyclohexylethyl)-N-p-nitrobenzenesulfonylaminomethyl)-2-(2-methylphenyl)benzoic acid methyl ester was converted into the title compound according to the procedures described in examples 608C and D to afford a colorless oil. MS(APCI(+)) 682 (M+H)⁺. MS(APCI(-)) 716 (M+Cl)⁻.

11225

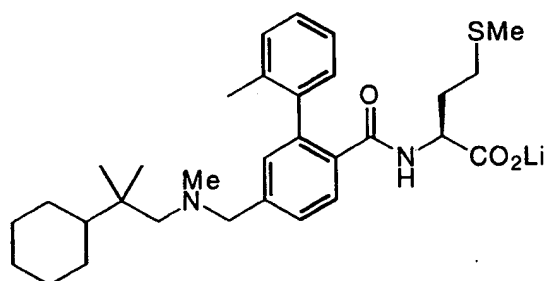
Example 1068D

N-[4-(N-(2-Cyclohexylethyl)-N-p-nitrobenzenesulfonylaminomethyl)-2-(2-methylphenyl)benzoyl]methionine, lithium salt

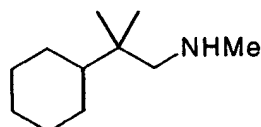
N-[4-(N-(2-Cyclohexylethyl)-N-p-nitrobenzenesulfonylaminomethyl)-2-(2-methylphenyl)benzoyl]methionine methyl ester was converted to the title compound according to the procedure described in example 608E, and was isolated as a white powder.

¹H NMR (300 MHz, DMSO) δ 0.63-0.76 (m, 2H), 1.00-1.26 (m, 6H), 1.40-1.70 (m, 10H), 1.92 (s, 3H), 1.95-2.15 (m, 3H), 3.12-3.20 (m, 2H), 3.59-3.65 (m, 1H), 4.43 (s, 2H), 6.96 (d, J=6.3 Hz, 1H), 7.0-7.25 (m, 5H), 7.36 (d, J=8.1 Hz, 1H), 7.52 (d, J=7.8 Hz, 1H), 8.13 (d, J=8.7 Hz, 2H), 8.37 (d, J=8.4 Hz, 2H).

MS (APCI(-)) m/e 667 (M⁻); Analysis calc'd for C₃₄H₄₀LiN₃O₇S₂•1.2H₂O: C, 58.73; H, 6.15; N, 6.04; found: C, 58.73; H, 5.82; N, 5.92.

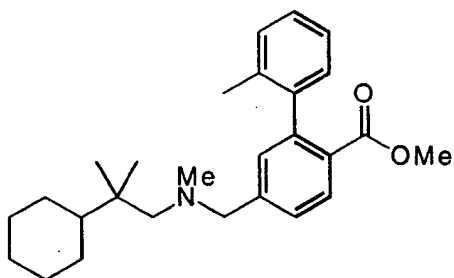
Example 1069

N-[4-(N-(2-Cyclohexyl-2-methylpropyl)-N-methylaminomethyl)-2-(2-methylphenyl)benzoyl]methionine, lithium salt

Example 1069A

N-Methyl-2-cyclohexyl-2-methylpropylamine

- 11250 Treatment of 2-phenyl-2-methylpropylamine (example 1048A, 5g) with di-tert-butylidicarbonate according to example 1056A afforded N-tert-butoxycarbonyl-2-phenyl-2-methylpropylamine (10g crude) as a colorless oil. To portion of this material (5g) in methanol (100mL) was added platinum oxide (1g), and the reaction was shaken under hydrogen gas (4atm) for 24h. The reaction was concentrated, diluted with water (100mL),
11255 and extracted with chloroform (3X50mL). The organic extracts were washed with brine (20mL), dried (MgSO₄), filtered and concentrated. The residue was purified by silica gel chromatography eluting with 10% EtOAc/hexane to afford a colorless oil (1.0g). This material was reduced with LiAlH₄ according to the procedure described in example 1056A to afford the title compound (0.8g), as a colorless oil.
- 11260 ¹H NMR (300 MHz, CDCl₃) δ 0.83 (s, 6H), 0.87-1.29 (m, 6H), 1.60-1.82 (m, 5H), 2.36 (s, 2H), 2.42 (s, 3H).
MS (APCI(+)) m/e 170 (M+H)⁺.

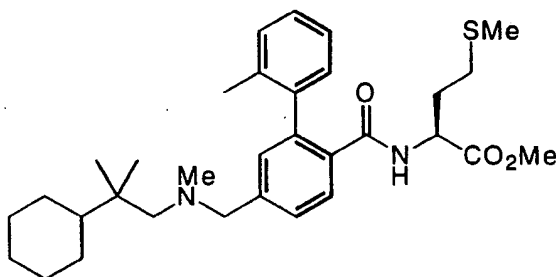


11265

Example 1069B

4-(N-(2-Cyclohexyl-2-methylpropyl)-N-methylaminomethyl)-2-(2-methylphenyl)benzoic acid, Methyl Ester

- The title compound was prepared according to the procedure in example 608B, substituting N-methyl-2-cyclohexyl-2-methylpropylamine for N-methylcyclohexylethylamine, and was isolated as a colorless oil. MS(ESI(+)) m/e 408 (M+H)⁺.
- 11270

Example 1069C

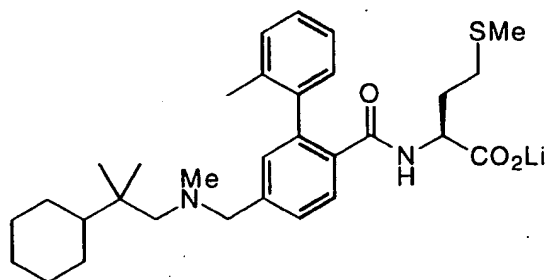
11275

N-[4-(N-(2-Cyclohexyl-2-methylpropyl)-N-methylaminomethyl)-2-(2-methylphenyl)benzoyl]methionine, Methyl Ester

The title compound was prepared from 4-(N-(2-cyclohexyl-2-methylpropyl)-N-methylaminomethyl)-2-(2-methylphenyl)benzoic acid methyl ester according to the procedures described in examples 608C, and D, and was isolated as a colorless oil.

11280

MS(ESI(+)) m/e 539 (M+H)⁺. MS(ESI(-)) m/e 537 (M-H)⁻.



Example 1069D

11285

N-[4-(N-(2-Cyclohexyl-2-methylpropyl)-N-methylaminomethyl)-2-(2-methylphenyl)benzoyl]methionine, lithium salt

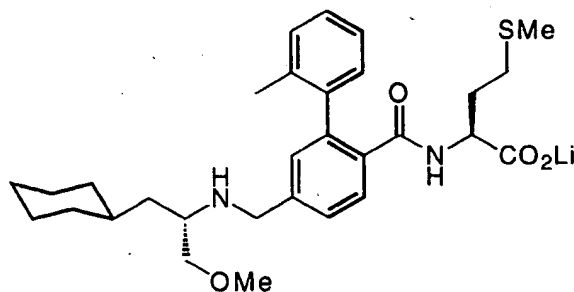
The title compound was prepared from N-[4-(N-(2-cyclohexyl-2-methylpropyl)-N-methylaminomethyl)-2-(2-methylphenyl)benzoyl]methionine methyl ester according to the procedure in example 608E, and was isolated as a white powder.

¹H NMR (300 MHz, DMSO) δ 0.79 (s, 6H), 0.80-1.27 (m, 5H), 1.50-1.74 (m, 6H), 1.75-2.95 (m, 7H), 1.92 (s, 3H), 2.19 (s, 3H), 2.24 (s, 2H), 3.56 (s, 2H), 3.62-3.72 (m, 1H), 6.92 (d, J=6 Hz, 1H), 7.08-7.25 (m, 5H); 7.36 (d, J=7.8 Hz, 1H), 7.49 (d, J=7.8 Hz, 1H).

11290

MS (ESI(-)) m/e 523 (M-H); Analysis calc'd for C₃₁H₄₃LiN₂O₃S•1.3H₂O: C, 67.70; H, 8.29; N, 5.06; found: C, 67.15; H, 8.08; N, 4.97.

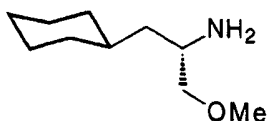
11295



Example 1070

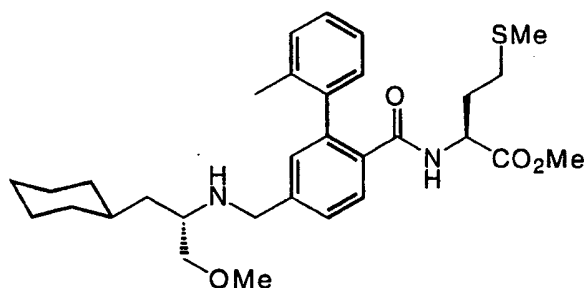
N-[4-(3-Cyclohexyl-1-methoxyprop-2-ylaminomethyl)-2-(2-methylphenyl)benzoyl]methionine, lithium salt

11300

Example 1070A(S)-3-Cyclohexyl-1-methoxy-2-propylamine

11305 To a solution of (S)-3-phenyl-1-methoxy-2-propylamine hydrochloride (0.5g) in ethanol (100ml) was added concentrated HCl (0.32mL), and platinum oxide (0.5g), and the reaction was shaken under hydrogen gas (4atm) for 18h. The reaction was filtered, concentrated, diluted with water (50mL) and neutralized with 1M NaOH (to pH \approx 11). The mixture was washed with chloroform (3X50mL), and the organic extracts were washed
11310 with brine (20mL), dried (MgSO₄), filtered and concentrated to give a colorless oil (400mg).

¹H NMR (300 MHz, CDCl₃) δ 0.76-1.00 (m, 2H), 1.10-1.48 (m, 6H), 1.61-1.81 (m, 5H), 3.01-3.14 (m, 2H), 3.30-3.35 (m, 1H), 3.36 (s, 3H).

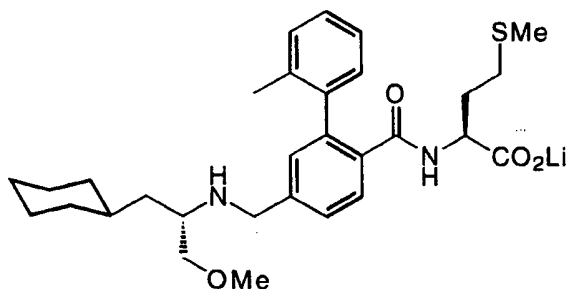


11315

Example 1070BN-[4-(3-Cyclohexyl-1-methoxyprop-2-ylaminomethyl)-2-(2-methylphenyl)benzoyl]methionine, Methyl Ester

11320 The title compound was prepared from (S)-3-cyclohexyl-1-methoxy-2-propylamine according to the procedure described in example 403H to afford a colorless oil.

MS(APCI(+)) 541 (M+H)⁺. MS(APCI(-)) 539 (M-H)⁻.

Example 1070C

11325

N-[4-(3-Cyclohexyl-1-methoxyprop-2-ylaminomethyl)-2-(2-methylphenyl)benzoyl]methionine, lithium salt

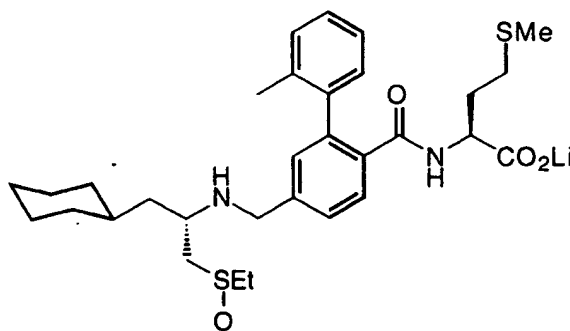
N-[4-(3-Cyclohexyl-1-methoxyprop-2-ylaminomethyl)-2-(2-methylphenyl)benzoyl]methionine methyl ester was converted into the title compound according to the procedure described in example 608E, affording a white powder.

11330

¹H NMR (300 MHz, DMSO) δ 0.65-0.88 (m, 2H); 1.00-1.88 (m, 15H), 1.91 (s, 3H), 1.95-2.19 (m, 3H), 2.61-2.68 (m, 1H), 3.20 (s, 3H), 3.20-3.26 (m, 2H), 3.62-3.84 (m, 3H), 6.85-7.00 (m, 2H), 7.09-7.24 (m, 5H), 7.36 (d, J=7.8 Hz, 1H), 7.48 (d, J=7.8 Hz, 1H).

11335

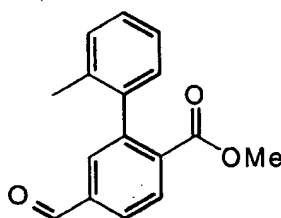
MS (APCI(-)) m/e 525 (M-H); Analysis calc'd for C₃₀H₄₁LiN₂O₄S•0.60H₂O: C, 66.30; H, 7.83; N, 5.15; found: C, 66.29; H, 7.69; N, 5.15.



Example 1071

11340

N-[4-(1-Ethylsulfenyl-3-cyclohexylprop-2-ylaminomethyl)-2-(2-methylphenyl)benzoyl]methionine, lithium salt



Example 1071A

11345

4-Formyl-2-(2-methylphenyl)benzoic acid methyl ester

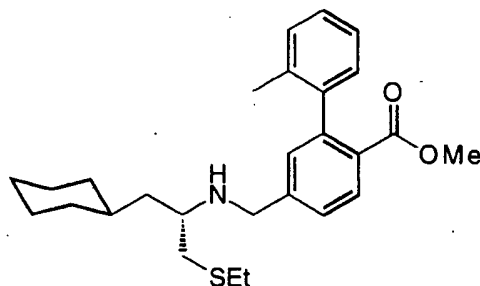
To a solution of 4-hydroxymethyl-2-(2-methylphenyl)benzoic acid methyl ester (example 1178C, 1.0g) in dichloromethane (10mL) was added infusorial earth (2g) then at 0°C was added pyridinium chlorochromate (1.7g). After 10min, the reaction was warmed to ambient temperature. After 1h, the reaction was diluted with ether (50mL), and filtered through infusorial earth. The solution was concentrated, and the residue was purified by

11350

silica gel chromatography eluting with 20% EtOAc/hexanes to afford the title compound as a colorless oil (0.842g, 85%).

^1H NMR (300 MHz, CDCl_3) δ 2.08 (s, 3H), 3.63 (s, 3H), 7.07 (brd, $J=6.6$ Hz, 1H), 7.19-7.30 (m, 3H), 7.76 (d, $J=1.8$ Hz, 1H), 7.93 (dd, $J=8.1, 1.6$ Hz, 1H), 8.06 (d, $J=8.1$ Hz, 1H), 10.09 (s, 1H).

MS (DCI/ NH_3) m/e 255 ($\text{M}+\text{H}$) $^+$.

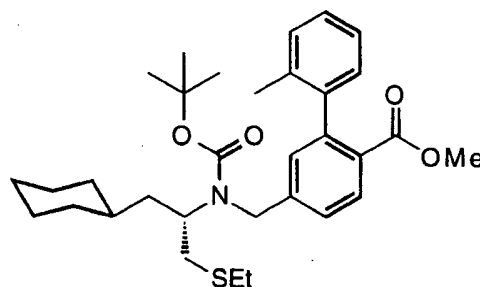


Example 1071B

4-N-(3-Cyclohexyl-1-ethylthioprop-2-yl)aminomethyl-2-(2-methylphenyl)benzoic acid, Methyl Ester

The title compound was prepared according to example 403H, substituting 4-formyl-2-(2-methylphenyl)benzoic acid methyl ester for N-[4-formyl-2-(2-methylphenyl)benzoyl]methionine methyl ester, to afford a colorless oil in 70% yield.

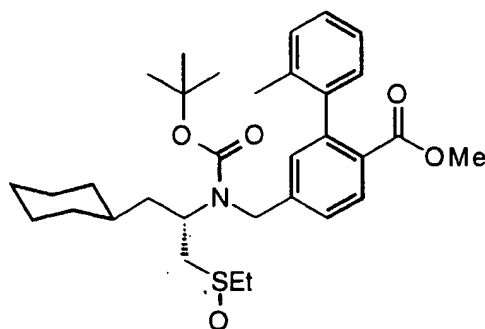
MS(APCI(+)) 440 ($\text{M}+\text{H}$) $^+$. MS(APCI(-)) 438 ($\text{M}-\text{H}$) $^-$.



Example 1071C

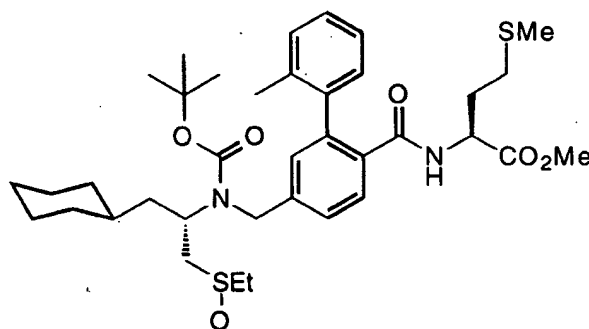
4-N-tert-Butoxycarbonyl-N-(3-cyclohexyl-1-ethylthioprop-2-yl)aminomethyl-2-(2-methylphenyl)benzoic acid, Methyl Ester

To a solution of 4-N-(3-cyclohexyl-1-ethylthioprop-2-yl)aminomethyl-2-(2-methylphenyl)benzoic acid methyl ester (497mg) in dichloromethane (4mL) was added di-tert-butyldicarbonate (300mg). After 16h at ambient temperature, the reaction was concentrated, and the residue was purified by silica gel chromatography eluting with 10% EtOAc/hexane to give the title compound as a colorless oil (605mg). MS(APCI(-)) 538 ($\text{M}-\text{H}$) $^-$.

Example 1071D

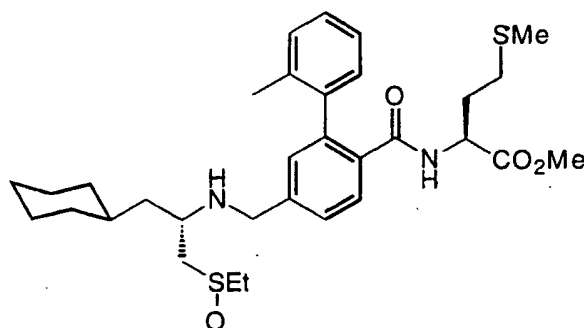
11380 4-N-tert-Butoxycarbonyl-N-(1-ethylsulfenyl-3-cyclohexylprop-2-ylaminomethyl)-2-(2-
methylphenyl)benzoic acid, Methyl Ester

To a solution of 4-N-tert-Butoxycarbonyl-N-(3-cyclohexyl-1-ethylthioprop-2-yl)aminomethyl-2-(2-methylphenyl)benzoic acid methyl ester (600mg) in dichloromethane (5mL) at -78°C was added m-chloroperbenzoic acid (280mg@75%). After 1.5h, the
 11385 reaction was warmed to 0°C, and after 30min, the reaction was quenched with dilute aqueous sodium sulfite. The product was extracted into EtOAc (30mL), and washed with sodium bicarbonate (3X5mL). The organic extracts were washed with brine (10mL), dried (MgSO₄), filtered and concentrated. The residue was purified by silica gel chromatography eluting with 50%-100% EtOAc/hexane to afford a white foam (460mg, 75%). MS(APCI(+))
 11390 556 (M+H)⁺. MS(APCI(-)) 590 (M+Cl)⁻.

Example 1071E

11395 N-tert-Butoxycarbonyl-N-[4-(1-ethylsulfenyl-3-cyclohexylprop-2-ylaminomethyl)-2-(2-
methylphenyl)benzoyl]methionine, Methyl Ester

The title compound was prepared from 4-(1-ethylsulfenyl-3-cyclohexylprop-2-ylaminomethyl)-2-(2-methylphenyl)benzoic acid methyl ester according to the procedure described in examples 608C and D to afford a colorless oil which was purified by silica gel chromatography eluting with 5% methanol/dichloromethane. MS(APCI(+)) 687 (M+H)⁺.
 11400 MS(APCI(-)) 721 (M+Cl)⁻.



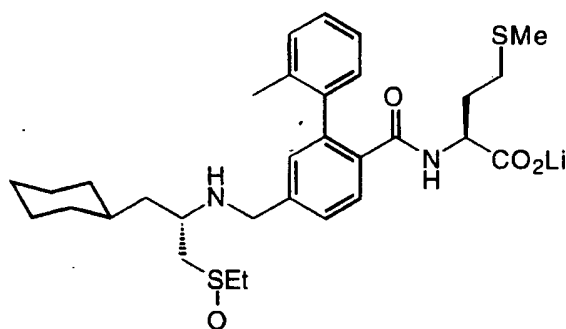
Example 1071F

N-[4-(1-ethylsulfenyl)-3-cyclohexylprop-2-ylaminomethyl]-2-(2-methylphenyl)benzoyl]methionine, Methyl Ester

11405

To a solution of N-tert-butoxycarbonyl-N-[4-(1-ethylsulfenyl)-3-cyclohexylprop-2-ylaminomethyl]-2-(2-methylphenyl)benzoyl]methionine methyl ester (200mg) in dioxane (1mL) chilled to its melting point, was added HCl (0.75mL, 4M in dioxane). After 1h, the reaction was quenched with excess aqueous sodium bicarbonate, and extracted into

11410 dichloromethane. The solution was concentrated, and the residue was purified by silica gel chromatography eluting with 5% methanol/dichloromethane to afford the title compound as a colorless oil (72mg, 42%). MS(APCI(+)) 587 (M+H)⁺. MS(APCI(-)) 621 (M+Cl)⁻.



11415

Example 1071G

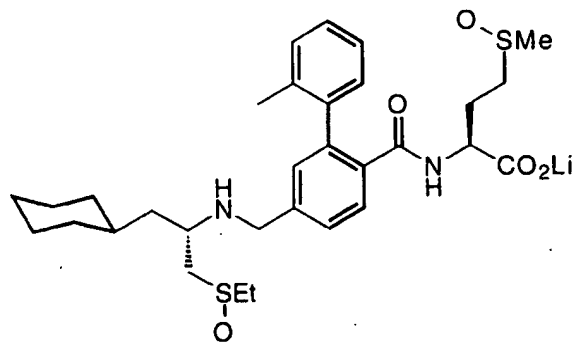
N-[4-(1-ethylsulfenyl)-3-cyclohexylprop-2-ylaminomethyl]-2-(2-methylphenyl)benzoyl]methionine, lithium salt

N-[4-(1-Ethylsulfenyl)-3-cyclohexylprop-2-ylaminomethyl]-2-(2-methylphenyl)benzoyl]methionine methyl ester was converted into the title compound according to the procedure described in example 608E.

11420

¹H NMR (300 MHz, DMSO) δ 0.67-0.93 (m, 2H), 1.00-1.90 (m, 13H), 1.11 (t, J=7.5 Hz, 3H), 1.94-2.20 (m, 6H), 2.34-2.45 (m, 5H), 2.56-2.67 (m, 2H), 3.62-3.83 (m, 3H), 6.98 (brd, J=6 Hz, 1H), 7.10-7.24 (m, 5H), 7.38 (brd, J=7.8 Hz, 1H), 7.49 (d, J=7.8 Hz, 0.5H), 7.5 (d, J=7.8 Hz, 0.5H).

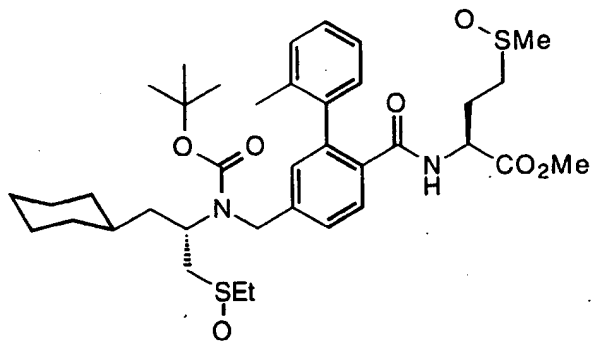
11425 MS (ESI(-)) m/e 571 (M-H).



Example 1072

11430

(2S)-2-N-[4-(1-ethylsulfenyl)-3-cyclohexylprop-2-ylaminomethyl]-2-(2-methylphenyl)benzoylamino-4-methylsulfenylbutanoate, lithium salt

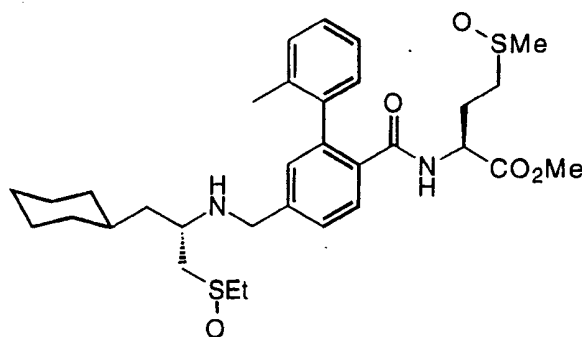


Example 1072A

11435 (2S)-N-tert-Butoxycarbonyl-2-N-[4-(1-ethylsulfenyl)-3-cyclohexylprop-2-ylaminomethyl]-2-(2-methylphenyl)benzoylamino-4-methylsulfenylbutanoate, Methyl Ester

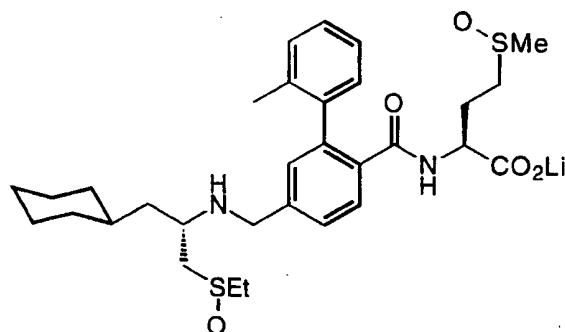
To a solution of N-tert-butoxycarbonyl-N-[4-(1-ethylsulfenyl)-3-cyclohexylprop-2-ylaminomethyl]-2-(2-methylphenyl)benzoyl]methionine methyl ester (example 1071E, 320mg) in dichloromethane (2mL) at -78°C was added m-chloroperbenzoic acid (120mg@75%). After 1.5h, the reaction was warmed to -50°C, and after 30min, the reaction was quenched with dilute aqueous sodium sulfite. The product was extracted into EtOAc (30mL), and washed with sodium bicarbonate (3X5mL). The organic extracts were washed with brine (10mL), dried (MgSO₄), filtered and concentrated. The residue was purified by silica gel chromatography eluting with 5% methanol/dichloromethane to afford a white foam (311mg, 95%). MS(APCI(+)) 703 (M+H)⁺. MS(APCI(-)) 737 (M+Cl)⁻.

11445

Example 1072B

(2S) 2-N-[4-(1-Ethylsulfenyl-3-cyclohexylprop-2-ylaminomethyl)-2-(2-methylphenyl)benzoyl]amino-4-methylsulfenylbutanoate, Methyl Ester

The title compound was prepared from (2S) N-tert-butoxycarbonyl-2-N-[4-(1-ethylsulfenyl-3-cyclohexylprop-2-ylaminomethyl)-2-(2-methylphenyl)benzoyl]amino-4-methylsulfenylbutanoate methyl ester according to the procedure described in example 1071F in 58% yield. The product was purified by silica gel chromatography eluting with 5%-10% methanol/dichloromethane, and was isolated as a white foam. MS(APCI(+)) 603 (M+H)⁺. MS(APCI(-)) 637 (M+Cl)⁻.

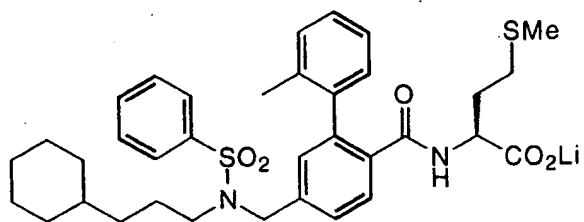
Example 1072C

(2S) 2-N-[4-(1-ethylsulfenyl-3-cyclohexylprop-2-ylaminomethyl)-2-(2-methylphenyl)benzoyl]amino-4-methylsulfenylbutanoate, lithium salt

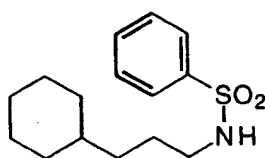
(2S) 2-N-[4-(1-Ethylsulfenyl-3-cyclohexylprop-2-ylaminomethyl)-2-(2-methylphenyl)benzoyl]amino-4-methylsulfenylbutanoate methyl ester was converted into the title compound according to the procedure described in example 608E, and was isolated as a yellow powder.

¹H NMR (300 MHz, DMSO) δ 0.72-0.90 (m, 2H), 1.03-1.20 (m, 5H), 1.20-1.90 (m, 11H), 1.94-2.23 (m, 5H), 2.36 (s, 3H), 2.57-2.80 (m, 4H), 2.98 (brs, 1H), 3.64-3.82 (m, 3H), 6.95-7.00 (m, 1H), 7.09-7.23 (m, 5H), 7.33-7.41 (m, 1H), 7.49 (d, J=8.1 Hz, 0.5H), 7.50 (d, J=8.1 Hz, 0.5H).

MS (ESI(-)) m/e 587 (M-H).

Example 1073

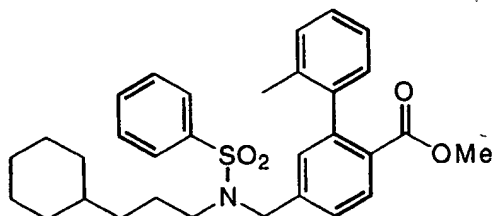
11475 N-[4-(N-(3-cyclohexylpropyl)-N-benzenesulfonylaminomethyl)-2-(2-methylphenyl)benzoyl]methionine, lithium salt

Example 1073A

11480 N-3-Cyclohexylpropylbenzenesulfonamide

The title compound was prepared according to example 1063A (replacing phenethylamine with 3-phenylpropylamine, and example 1063B, replacing p-toluenesulfonyl chloride with benzenesulfonyl chloride to afford a colorless oil.

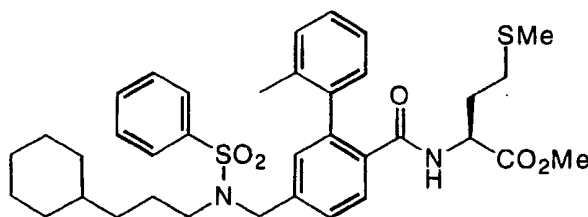
MS (DCI/NH₃) m/e 299 (M+NH₄)⁺.

Example 1073B

4-(N-(3-cyclohexylpropyl)-N-benzenesulfonylaminomethyl)-2-(2-methylphenyl)benzoic acid, Methyl Ester

11490 N-3-Cyclohexylpropylbenzenesulfonamide was converted into the title compound according to the procedure in example 1063C to afford a colorless oil.

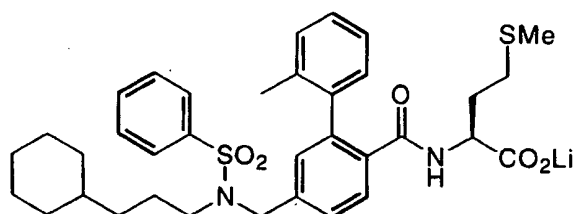
MS (DCI/NH₃) m/e 537 (M+NH₄)⁺.



Example 1073C

N-[4-(N-(3-cyclohexylpropyl)-N-benzenesulfonylaminomethyl)-2-(2-methylphenyl)benzoyl]methionine, Methyl Ester

4-(N-(3-Cyclohexylpropyl)-N-benzenesulfonylaminomethyl)-2-(2-methylphenyl)benzoic acid methyl ester was converted into the title compound according to the procedures described in examples 608C and D to afford a colorless oil. MS(ESI(+)) 651 (M+H)⁺. MS(ESI(-)) 649 (M-H)⁻.

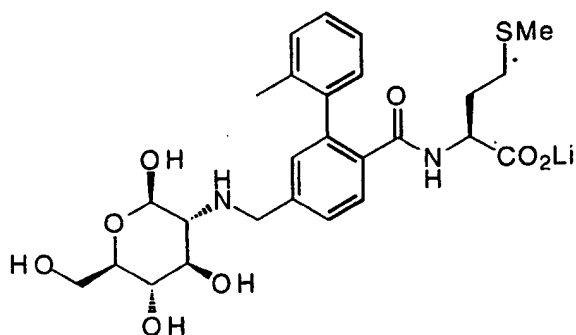


Example 1073D

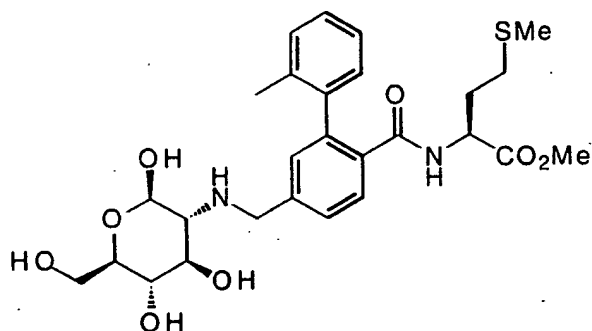
N-[4-(N-(3-cyclohexylpropyl)-N-benzenesulfonylaminomethyl)-2-(2-methylphenyl)benzoyl]methionine, lithium salt

N-[4-(N-(3-Cyclohexylpropyl)-N-benzenesulfonylaminomethyl)-2-(2-methylphenyl)benzoyl]methionine methyl ester was converted to the title compound according to the procedure described in example 608E, and was isolated as a white powder. ¹H NMR (300 MHz, DMSO) δ 0.59-0.73 (m, 2H), 0.88-1.88 (m, 17H), 1.94 (s, 3H), 1.95-2.16 (m, 3H), 3.00-3.08 (m, 2H), 3.59-3.68 (m, 1H), 4.39 (s, 2H), 6.96 (d, J=6 Hz, 1H), 7.04-7.28 (m, 5H), 7.36 (d, J=7.8 Hz, 1H), 7.51 (d, J=7.8 Hz, 1H), 7.56-7.70 (m, 3H), 7.85 (d, J=6.9 Hz, 2H).

MS (ESI(-)) m/e 635 (M-H); Analysis calc'd for C₃₅H₄₃LiN₂O₅S₂•1.65H₂O: C, 62.51; H, 6.94; N, 4.17; found: C, 62.48; H, 6.79; N, 4.07.

Example 1074

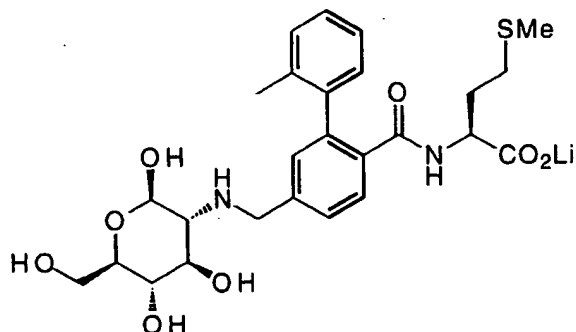
11520

N-[4-(N-glucosaminomethyl)-2-(2-methylphenyl)benzoyl]methionine, lithium saltExample 1074AN-[4-(N-glucosaminomethyl)-2-(2-methylphenyl)benzoyl]methionine, Methyl Ester

11525

A 1M solution of glucosamine was prepared by dissolving glucosamine•HCl (10g) in 1M NaOH (47mL). This solution (0.31 mL) was added to N-[4-formyl-2-(2-methylphenyl)benzoyl] methionine methyl ester (example 403G, 100mg), in ethanol (3mL). Once dissolution was complete, the reaction was degassed, and 10% palladium on carbon (330mg) was added, followed by blanketing the reaction with a hydrogen atmosphere (1atm). After 4h, the reaction was filtered and concentrated, and the residue was purified by silica gel chromatography eluting with 20% methanol/dichloromethane to give the title compound as a colorless syrup (50mg, 35%). MS(ESI(+)) 549 (M+H)⁺, 571 (M+Na)⁺.

11530

Example 1074B

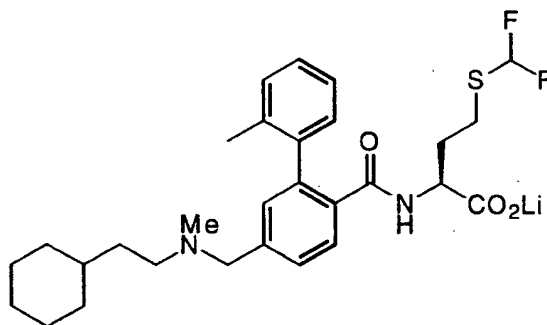
11535

N-[4-(N-glucosaminomethyl)-2-(2-methylphenyl)benzoyl]methionine, lithium salt

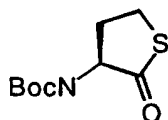
The title compound was prepared from N-[4-(N-Glucosaminomethyl)-2-(2-methylphenyl)benzoyl]methionine methyl ester according to the procedure described in example 608E, and was isolated as a fluffy white powder.

11540 ¹H NMR (300 MHz, CD₃OD) δ 1.60-1.90 (m, 4H), 1.95-2.09 (m, 6H), 2.26 (brs, 2H), 2.41 (brt, J=9.3 Hz, 1H), 2.54 (dd, J=10.2, 3.3 Hz, 1H), 3.22-3.30 (m, 2H), 3.58-4.03 (m, 5H), 4.13-4.28 (m, 2H), 4.58 (d, J=7.8 Hz, 1H), 5.17-5.22 (m, 1H), 7.07-7.30 (m, 6H), 7.42-7.47 (m, 1H), 7.61-7.67 (m, 1H).
MS (ESI(-)) m/e 533 (M-H).

11545

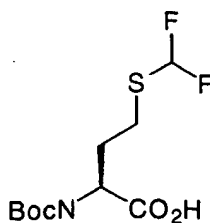
Example 1079

11550 (2S) 2-N-[4-(N-2-Cyclohexylethyl)-N-methylaminomethyl)-2-(2-methylphenyl)benzoyl]amino-4-difluoromethylthiobutanoate, lithium salt

Example 1079AN-tert-Butoxycarbonylhomocysteine thiolactone

11555 To a solution of L-homocysteinethiolactone hydrochloride (560mg) in dioxane (10mL) was added triethylamine (0.6mL), and di-tert-butyl dicarbonate (874mg). After 20h, the reaction was diluted with EtOAc (100mL), washed with water (20mL), 1M HCl (20mL), and again with water (2X20mL). The organic extracts were washed with brine (20mL), dried (MgSO₄), filtered and concentrated to give a white crystalline solid.

11560 ¹H NMR (300 MHz, CDCl₃) δ 1.45 (s, 9H), 1.97 (ddd, J=25, 11.7, 6.6 Hz, 1H), 2.86 (m, 1H), 3.23 (dd, J=11.4, 1.5 Hz, 1H), 3.32 (ddd, J=11.4, 11.4, 5.1 Hz, 1H), 4.28 (m, 1H), 4.98 (brs, 1H).

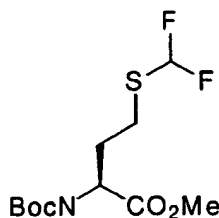
Example 1079BN-tert-Butoxycarbonyl-S-difluoromethylhomocysteine

To a solution of N-tert-butoxycarbonylhomocysteine thiolactone hydrochloride (400mg) in THF (2mL) at 0°C was added 1M NaOH (6mL). After stirring for 20min, this solution was added to chlorodifluoromethane (≈0.25mL) at -78°C in a pressure tube. The vessel was sealed, and warmed to 60°C for 14h. The reaction was chilled to -78°C, opened, and warmed to ambient temperature. The aqueous solution was neutralized with 1M HCl, and extracted into dichloromethane (30mL). The organic extracts were washed with brine (20mL), dried (MgSO₄), filtered and concentrated to give the title compound as a syrup (490mg).

¹H NMR (300 MHz, CDCl₃) δ 1.45 (s, 9H), 1.95-2.36 (m, 2H), 2.63 (q, J=7.4 Hz, 1H), 2.90 (ddd, J=7.6, 7.6, 2.7 Hz, 1H), 4.46 (brs, 1H), 5.05 (brs, 1H), 6.82 (t, J=56 Hz, 1H).

MS (ESI(+)) m/e 308 (M+Na)⁺.

MS (ESI(-)) m/e 285 (M-H)⁻.

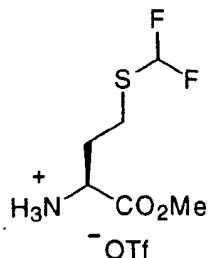
Example 1079CN-tert-Butoxycarbonyl-S-difluoromethylhomocysteine, Methyl Ester

To a solution of N-tert-butoxycarbonyl-S-difluoromethylhomocysteine in diethyl ether (1mL) was added a solution of diazomethane in ether until a faint yellow color persisted. The excess reagent was quenched by addition of glacial acetic acid, and the reaction was concentrated. The residue was purified by silica gel chromatography eluting with 20% EtOAc/hexane to afford a colorless oil (400mg).

¹H NMR (300 MHz, CDCl₃) δ 1.45 (s, 9H), 1.90-2.30 (m, 2H), 2.85 (t, J=7.5 Hz, 2H), 3.77 (s, 3H), 4.42 (brs, 1H), 5.08 (brs, 1H), 6.81 (t, J=56.1 Hz, 1H).

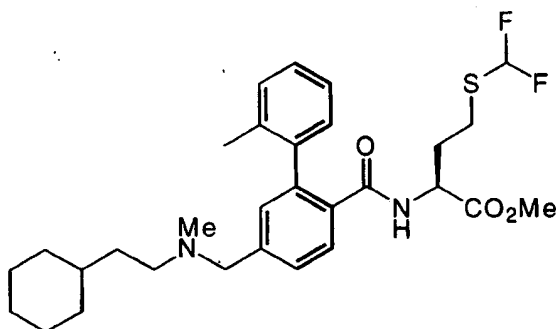
MS (ESI(+)) m/e 322 (M+Na)⁺.

MS (ESI(-)) m/e 298 (M-H)⁻.

Example 1079DS-difluoromethylhomocysteine, Methyl Ester, Trifluoroacetate

To a solution of N-tert-butoxycarbonyl-S-difluoromethylhomocysteine methyl ester (400mg) in dichloromethane (2mL) was added trifluoroacetic acid (1mL). After stirring 18h at ambient temperature, the reaction was concentrated, and the residue was triturated with toluene and evaporated to give the title compound as a tan solid (515mg).

¹H NMR (300 MHz, CDCl₃) δ 2.20-2.40 (m, 2H), 3.00 (t, J=7.5 Hz, 2H), 3.84 (s, 3H), 4.22 (t, J=6.9 Hz, 1H), 6.83 (t, J=55.8 Hz, 1H).

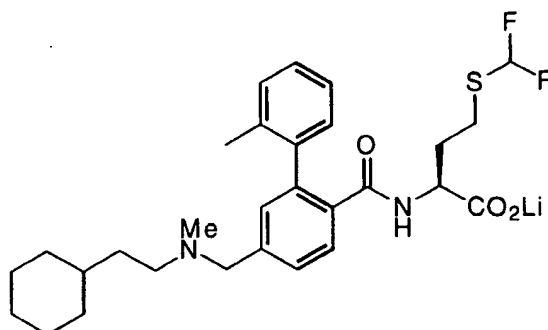
Example 1079E(2S)-2-N-[4-(N-2-Cyclohexylethyl-N-methylaminomethyl)-2-(2-methylphenyl)benzoyl]amino-4-difluoromethylthiobutanoate, Methyl Ester

The title compound was prepared according to the procedure in example 608D, replacing L-methionine methyl ester·HCl with S-difluoromethylhomocysteine methyl ester, trifluoroacetate, and was isolated as a colorless oil.

¹H NMR (300 MHz, CDCl₃) δ 0.80-0.94 (m, 2H), 1.10-1.70 (m, 11H), 1.90-2.18 (m, 5H), 2.20 (s, 3H), 2.30-2.41 (m, 4H), 3.53 (s, 2H), 3.67 (s, 3H), 4.57-5.66 (m, 1H), 5.83-5.90 (m, 1H), 6.73 ("dt", J=2.7, 56 Hz, 1H), 7.14-7.41 (m, 5H), 7.39 (brd, J=7.5 Hz, 1H), 7.90 ("dd", J=14.4, 8.1 Hz, 1H).

MS (ESI(+)) m/e 547 (M+H)⁺.

MS (ESI(-)) m/e 545 (M-H)⁻.

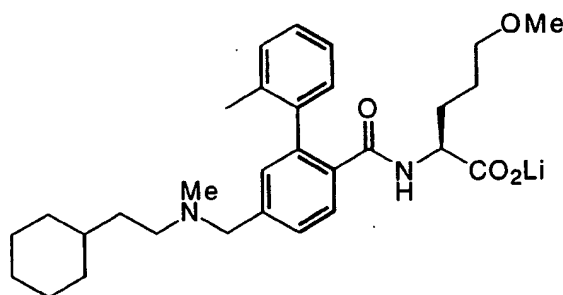
Example 1079F

11620 (2S) 2-N-[4-(N-2-Cyclohexylethyl-N-methylaminomethyl)-2-(2-
methylphenyl)benzoyl]amino-4-difluoromethylthiobutanoate, lithium salt

The title compound was prepared from (2S) 2-N-[4-(N-2-cyclohexylethyl-N-methylaminomethyl)-2-(2-methylphenyl)benzoyl]amino-4-difluoromethylthiobutanoate methyl ester according to the procedure described in example 608E with the following
 11625 exceptions: The crude lithium salt was found to be substantially impure by analytical HPLC, and was therefore purified by preparative reverse-phase medium pressure liquid chromatography eluting with a gradient of methanol/water/0.1%TFA. The appropriate fractions were concentrated, dissolved in water (10mL), neutralized (pH≈6) with sodium bicarbonate solution, then extracted into chloroform (30mL). The organic extracts were
 11630 washed with brine (20mL), dried (MgSO₄), filtered and concentrated. The free amino acid was dissolved in water, the lithium salt was prepared by addition of one equivalent of 5M LiOH, and the solution was frozen (-78°C) and lyophilized to give the title compound as a light yellow powder.

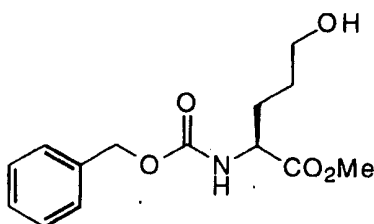
¹H NMR (300 MHz, DMSO) δ 0.75-0.90 (m, 2H), 1.06-1.38 (m, 6H), 1.53-1.80 (m, 9H), 1.94-2.16 (m, 3H), 2.13 (s, 3H), 2.34 (t, J=6 Hz, 2H), 3.49 (s, 2H), 3.60-3.75 (m, 1H), 6.91-7.23 (m, 7H), 7.23 (d, J=7.8 Hz, 1H), 7.50 (d, J=7.8 Hz, 1H).

MS (ESI(-)) m/e 531 (M-H).

Example 1080

11640

(2S) 2-N-[4-(N-2-Cyclohexylethyl-N-methylaminomethyl)-2-(2-methylphenyl)benzoyl]amino-5-methoxypentanoate, lithium salt



11645

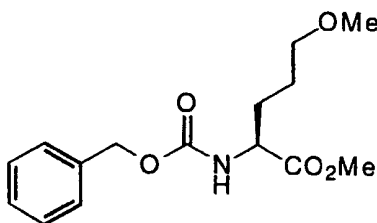
Example 1080A

Methyl (2S)-N-2-Carbobenzyloxyamino-5-hydroxypentanoate

To a solution of N-carbobenzyloxy-L-glutamic acid 1-methyl ester (commercial, 1.0g) in 3.5mL THF at 0°C was added 1M BH₃•THF (6.7mL). After 1h, the reaction was quenched by addition of 1M sodium bisulfate (10mL), and concentrated. The reaction was diluted with water (20mL) and the product was extracted into EtOAc (50mL). The organic extracts were washed with brine (20mL), dried (MgSO₄), filtered and concentrated. The residue was purified by silica gel chromatography eluting with 100% EtOAc to afford a colorless oil (500mg).

MS (ESI(+)) m/e 282 (M+H)⁺, 299 (M+NH₄)⁺.

MS (ESI(-)) m/e 280 (M-H)⁻.



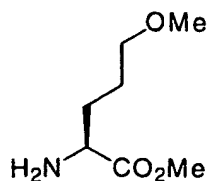
Example 1080B

Methyl (2S)-N-2-Carbobenzyloxyamino-5-methoxypentanoate

Methyl (2S)-N-2-carbobenzyloxyamino-5-hydroxypentanoate (500mg) was dissolved in ether (10mL), followed by addition of silica gel (2g). Diazomethane solution in ether was added (≈20mL), without observing the persistence of the yellow color of the reagent. The reaction was filtered and concentrated, and the above procedure was repeated. The residue was purified by silica gel chromatography eluting with 50% EtOAc/hexane to afford a colorless oil (236mg, 45%). The yield reflects the poor conversion of the reaction. ¹H NMR (300 MHz, CDCl₃) δ 1.59-2.00 (m, 4H), 3.31 (s, 3H), 3.38 (t, J=6 Hz, 2H), 3.74 (s, 3H), 4.34-4.44 (m, 1H), 5.11 (s, 2H), 5.43 (brd, J=7.8 Hz, 1H), 7.32-7.40 (m, 5H).

MS (ESI(+)) m/e 296 (M+H)⁺, 318 (M+Na)⁺.

MS (ESI(-)) m/e 294 (M-H)⁻.



Example 1080C

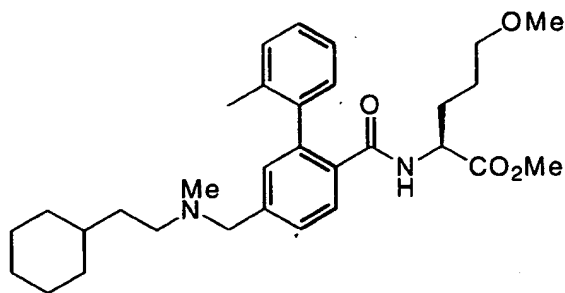
11675

Methyl (2S)-2-amino-5-methoxypentanoate

11680

Methyl (2S)-N-2-carbobenzyloxyamino-5-methoxypentanoate (230mg) was dissolved in methanol (2.5mL) at ambient temperature, followed by addition of ammonium formate (196mg), and 10% palladium on carbon (20mg). The reaction was refluxed for 30min, then cooled, filtered and concentrated. The residue was partitioned between dichloromethane and dilute NaOH. The organic extracts were washed with brine (10mL), dried (MgSO₄), filtered and concentrated to give the title compound (99mg, 78%) as a light yellow syrup.

MS (ESI(+)) m/e 162 (M+H)⁺.



11685

Example 1080D

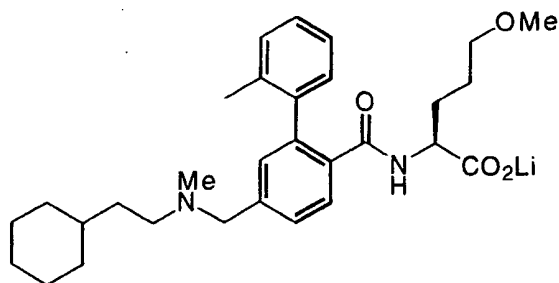
(2S) 2-N-[4-(N-2-Cyclohexylethyl-N-methylaminomethyl)-2-(2-methylphenyl)benzoyl]amino-5-methoxypentanoate, Methyl Ester

11690

The title compound was prepared according to example 608D, replacing L-methionine methyl ester-HCl with methyl (2S)-2-amino-5-methoxypentanoate, and was isolated as a colorless oil.

MS (ESI(+)) m/e 509 (M+H)⁺.

MS (ESI(-)) m/e 507 (M-H)⁻.



11695

Example 1080E

(2S) 2-N-[4-(N-2-Cyclohexylethyl-N-methylaminomethyl)-2-(2-methylphenyl)benzoyl]amino-5-methoxypentanoate, lithium salt

11700

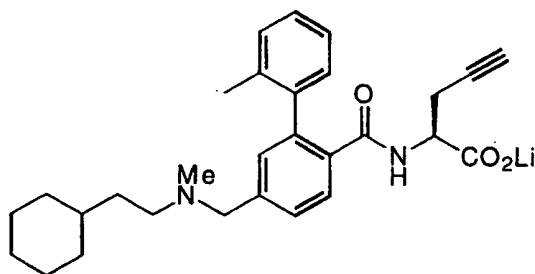
(2S) 2-N-[4-(N-2-Cyclohexylethyl-N-methylaminomethyl)-2-(2-methylphenyl)benzoyl]amino-5-methoxypentanoate methyl ester was converted to the title compound according to the procedure in example 608E, and was isolated as a white powder.

11705

¹H NMR (300 MHz, DMSO) δ 0.74-0.90 (m, 2H), 0.92-1.66 (m, 15H), 1.93-2.14 (m, 3H), 2.13 (s, 3H), 2.34 (t, J=6 Hz, 2H), 3.04-3.12 (m, 2H), 3.17 (s, 3H), 3.49 (s, 2H), 3.58-3.67 (m, 1H), 6.88-6.93 (m, 1H), 7.03-7.23 (m, 5H), 7.30 (d, J=8.1 Hz, 1H), 7.48 (d, J=8.1 Hz, 1H).

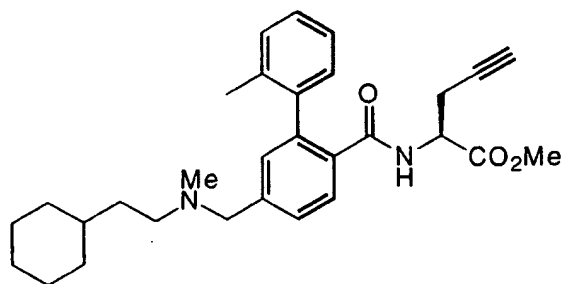
MS (ESI(-)) m/e 493 (M-H); Analysis calc'd for C₃₀H₄₁LiN₂O₄•0.75H₂O: C, 70.09; H, 8.33; N, 5.45; found: C, 70.4; H, 8.20; N, 5.38.

11710

Example 1081

(2S) 2-N-[4-(N-2-Cyclohexylethyl-N-methylaminomethyl)-2-(2-methylphenyl)benzoyl]aminopent-4-ynoate, lithium salt

11715

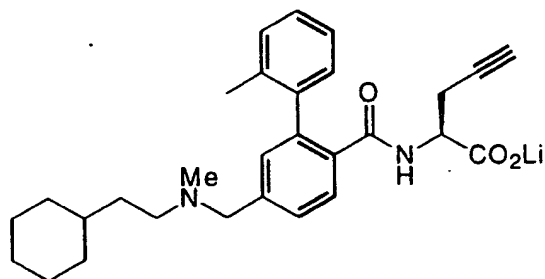
Example 1081A(2S) 2-N-[4-(N-2-Cyclohexylethyl-N-methylaminomethyl)-2-(2-methylphenyl)benzoyl]aminopent-4-ynoate, Methyl Ester

11720 The title compound was prepared according to example 608D, replacing L-methionine methyl ester·HCl with L-propargylalanine methyl ester·HCl, and was isolated as a colorless oil.

MS (ESI(+)) m/e 475 (M+H)⁺.

MS (ESI(-)) m/e 473 (M-H)⁻.

11725

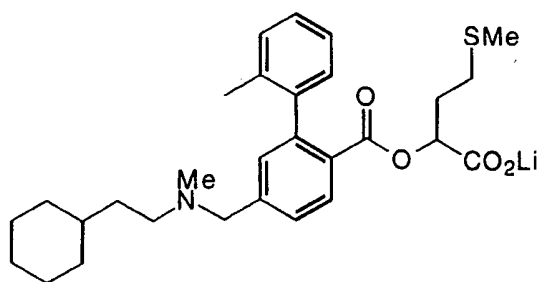
Example 1081B(2S) 2-N-[4-(N-2-Cyclohexylethyl-N-methylaminomethyl)-2-(2-methylphenyl)benzoyl]aminopent-4-ynoate, lithium salt

11730 (2S) 2-N-[4-(N-2-Cyclohexylethyl-N-methylaminomethyl)-2-(2-methylphenyl)benzoyl]aminopent-4-ynoate methyl ester was converted to the title compound according to the procedure in example 608E, and was isolated as a white powder.

¹H NMR (300 MHz, DMSO) δ 0.74-0.92 (m, 2H), 1.06-1.38 (m, 6H), 1.53-1.66 (m, 5H), 2.04 (s, 3H), 2.10 (m, 1H), 2.14 (s, 3H), 2.32 (t, J=6 Hz, 2H), 2.36-2.43 (m, 2H), 11735 3.49 (s, 2H), 3.56-3.63 (m, 1H), 7.00-7.28 (m, 6H), 7.31 (d, J=7.8 Hz, 1H), 7.52 (d, J=7.8 Hz, 1H).

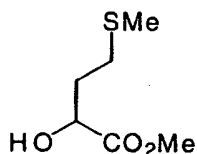
MS (ESI(-)) m/e 459 (M-H); Analysis calc'd for C₂₉H₃₅LiN₂O₃·1.90H₂O: C, 69.56; H, 7.81; N, 5.59; found: C, 69.49; H, 7.33; N, 5.57.

11740

Example 1082

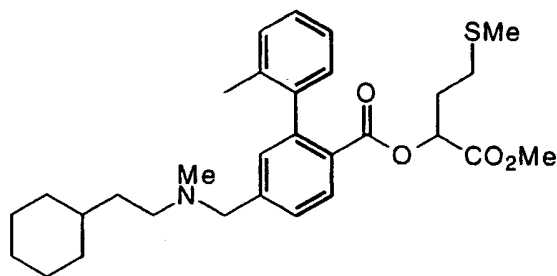
2-[4-(N-2-Cyclohexylethyl)-N-methylaminomethyl]-2-(2-methylphenyl)benzoyl]oxy-4-methylthiobutanoate, lithium salt

11745

Example 1082ADL, 2-Hydroxy-4-methylmercaptobutyric acid, Methyl Ester

A solution of DL, 2-hydroxy-4-methylmercaptobutyric acid calcium salt (2.2g) in 0.5M HCl (50mL) was saturated with sodium chloride, extracted exhaustively with EtOAc, which was dried (MgSO₄), filtered and concentrated. The residue was dissolved in methanol (10mL) and trimethylsilyldiazomethane (2M in hexane) was added until the yellow color persisted for 30min. The reaction was quenched by addition of glacial acetic acid and concentrated. The residue was purified by silica gel chromatography eluting with 30% EtOAc/hexane to give the title compound as a light yellow oil (1.37g).

¹H NMR (300 MHz, CDCl₃) δ 1.86-1.98 (m, 1H), 2.04-2.16 (m, 1H), 2.11 (s, 3H), 2.63 (d, J=7.8 Hz, 1H), 2.65 (dd, J=7.8, 1.5 Hz, 1H), 2.88 (brs, 1H), 3.81 (s, 3H), 3.34 (dd, J=7.8, 3.9 Hz, 1H).

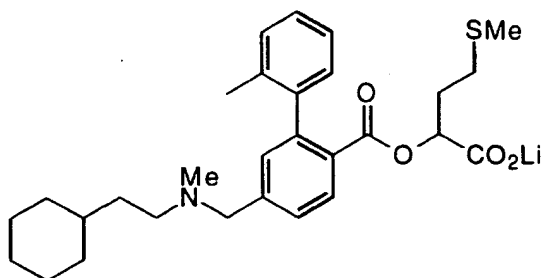


11760

Example 1082B

2-[4-(N-2-Cyclohexylethyl)-N-methylaminomethyl]-2-(2-methylphenyl)benzoyl]oxy-4-methylthiobutanoate, Methyl Ester

To a solution of DL, 2-hydroxy-4-methylmercaptobutyric acid methyl ester (72mg) and N-[4-(N-(2-cyclohexylethyl)-N-methylaminomethyl)-2-(2-methylphenyl)benzoic acid (example 608C, 150mg) in THF (1.0mL) was added triphenylphosphine (127mg) and diethyl azodicarboxylate (0.075mL). After 6h, the reaction was concentrated, and the residue was purified by silica gel chromatography eluting with 20% EtOAc/hexane to give the title compound as a colorless oil (90mg, 43%). MS(APCI(+)) 512 (M+H)⁺.



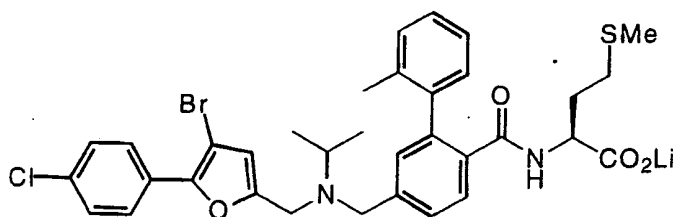
Example 1082C

2-[4-(N-2-Cyclohexylethyl-N-methylaminomethyl)-2-(2-methylphenyl)benzoyl]oxy-4-methylthiobutanoate, lithium salt

2-[4-(N-2-Cyclohexylethyl-N-methylaminomethyl)-2-(2-methylphenyl)benzoyl]oxy-4-methylthiobutanoate methyl ester (180mg) was dissolved in methanol (1.2mL) and 5M LiOH (0.088mL) was added, followed by addition of THF (0.5mL) to homogenize the reaction. After 4h, additional 5M LiOH (0.088mL) was added. After 1.5h, the reaction was concentrated, and the residue was dissolved in water (40mL). The aqueous solution was washed once with ether (20mL), then acidified, and the product was extracted into chloroform (3X20mL). The organic extracts were washed with brine (20mL), dried (MgSO₄), filtered and concentrated to give an oily foam (123mg). This residue was dissolved in 1:1 acetonitrile/water (30mL), and 5M LiOH (0.05mL) was added. The solution was frozen (-78°C) and lyophilized to afford the title compound as a very hygroscopic white powder (104mg).

¹H NMR (300 MHz, DMSO) δ 0.76-0.89 (m, 2H), 1.06-1.37 (m, 6H), 1.53-1.68 (m, 7H), 1.93-2.10 (m, 7H), 2.13 (s, 3H), 2.32 (t, J=7.2 Hz, 2H), 3.52 (s, 2H), 4.56-4.66 (m, 1H), 6.93-7.02 (m, 1H), 7.02-7.24 (m, 5H), 7.36-7.41 (m, 1H), 7.82 (d, J=7.8 Hz, 0.3H), 7.87 (d, J=7.8 Hz, 0.7H).

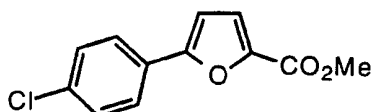
MS (APCI(-)) m/e 496 (M-H); Analysis calc'd for C₂₉H₃₈NO₄SLi•1.65H₂O: C, 65.31; H, 7.80; N, 2.63; found: C, 65.36; H, 7.76; N, 2.57.



11795

Example 1085

N-[4-(N-(5-bromo-(4-chlorophenyl)furan-2-ylmethyl)-N-isopropylaminomethyl)-2-(2-methylphenyl)benzoyl]methionine, lithium salt



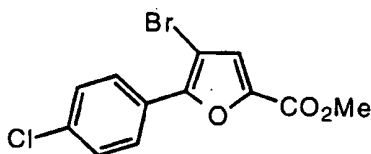
11800

Example 1085A

5-(4-chlorophenyl)-2-furoic acid, methyl ester

To a solution of 5-(4-chlorophenyl)-2-furoic acid (5.0 g, 22 mmol) in MeOH (50 mL) was added conc. H₂SO₄ (4 drops) and the resulting solution heated to 50 °C for 4 days. The reaction was cooled and concentrated in vacuo. The residue was taken up in EtOAc (100 mL) and washed with saturated aqueous NaHCO₃ (2 x 20 mL), dried (MgSO₄) and concentrated in vacuo. The residue was purified by flash chromatography (hexane/EtOAc 19:1) to give 3.8 g (72%) of a cream powder; MS m/z 254 (M⁺ + 18, 100).

11805



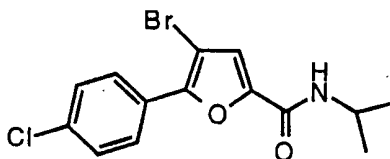
11810

Example 1085B

5-(4-chlorophenyl)-4-bromo-2-furoic acid, methyl ester

To a stirred solution of the ester (3.53 g, 14.9 mmol) in CHCl₃ (40 mL) was added a 4.2 M solution of Br₂ in CHCl₃ (4.3 mL, 17.9 mmol) and the resulting solution heated to 50 °C overnight. The reaction was concentrated in vacuo and the residue was purified by flash chromatography (hexane EtOAc 19:1) to give 3.0 g (64%) of a white powder; MS m/z 334 (M⁺ + 18, 100).

11815



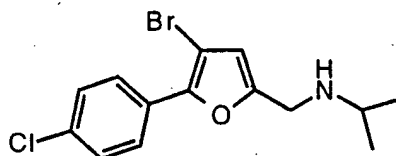
11820

Example 1085C

The ester (1.37 g, 4.34 mmol) was hydrolyzed as in example 1084 D (for 1 hour at rt) and coupled to isopropylamine as in example 1084 D to give 1.31 g (88 %) of a beige powder;

MS m/z 361 ($M^+ + 18$, 100).

11825

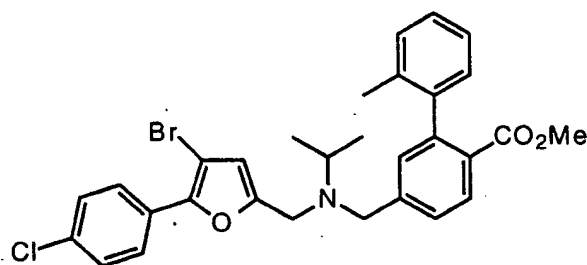
Example 1085C

11830

To a stirred solution of the amide (1.12 g, 3.27 mmol) in dichloroethane (50 mL) was added tetrabutylammonium borohydride (2.5 g, 9.8 mmol) and the resulting solution heated to 50 °C overnight. The reaction was concentrated in vacuo and the residue taken up in EtOAc (50 mL) and quenched with water (20 mL). The layers were separated and the organic layer washed with H₂O (20 mL) and brine (20 mL), dried (MgSO₄) and concentrated in vacuo. The residue was purified by flash chromatography

11835

(hexane/EtOAc 2:1) to give 0.49 g (46%) of a light yellow oil;
MS m/z 330 ($M^+ + 1$, 100).

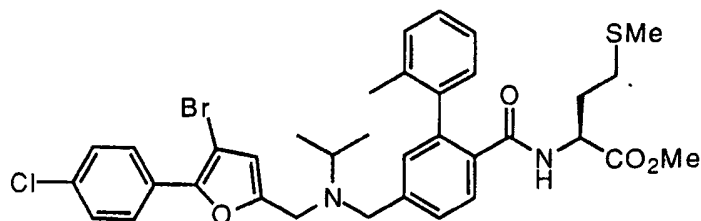
Example 1085D

11840

To a stirred solution of the amine (0.485 g, 1.48 mmol) in acetonitrile (10 mL) was added the core benzyl bromide (see example 1178D) (0.472 g, 1.48 mmol), tetrabutylammonium iodide (0.055 g, 0.15 mmol), and K₂CO₃ (0.41 g, 3.0 mmol) and the resulting solution heated to 70 °C overnight. The reaction was cooled and concentrated in vacuo. The residue was taken up in EtOAc (30 mL) and washed with H₂O (10 mL), saturated aqueous NaHCO₃ (10 mL), brine (10 mL), dried (MgSO₄) and concentrated in vacuo. The residue was purified by column chromatography (hexane/EtOAc 19:1) to give 0.63 g (75%) of a light yellow oil;

11845

MS m/z 568 ($M^+ + 1$, 100).

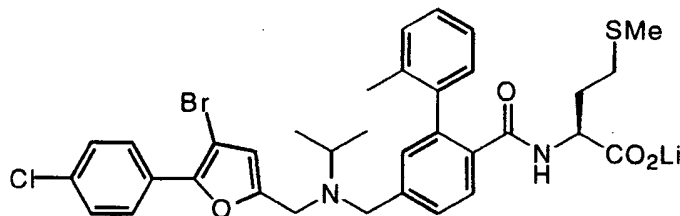


11850

Example 1085E

N-[4-(N-(5-bromo-(4-chlorophenyl)furan-2-yl)methyl)-N-isopropylaminomethyl]-2-(2-methylphenyl)benzoyl]methionine, methyl ester

The ester (0.61 g, 1.1 mmol) was hydrolyzed as in example 1084 D and coupled to
 11855 L-methionine methyl ester hydrochloride as in example 1084 D. Flash chromatography (hexane/EtOAc 4:1) gave 0.57 g (77 %) of an orange oil;
 MS m/z 697 ($M^+ + 1$, 100).



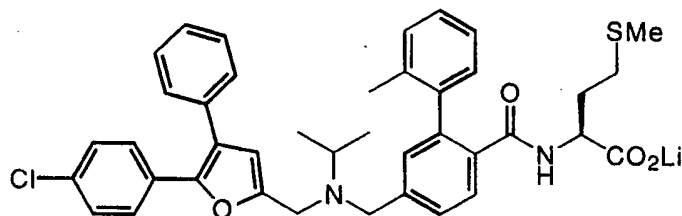
11860

Example 1085F

N-[4-(N-(5-bromo-(4-chlorophenyl)furan-2-yl)methyl)-N-isopropylaminomethyl]-2-(2-methylphenyl)benzoyl]methionine, lithium salt

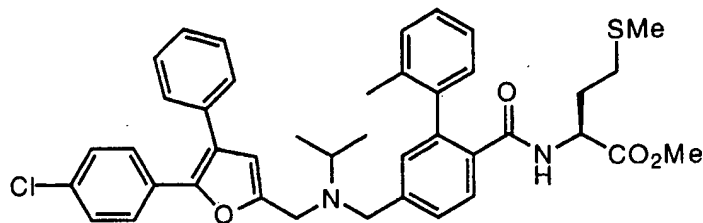
The ester (54 mg, 0.077 mmol) was hydrolyzed as in example 1084 E to give 53 mg
 of a beige powder;
 11865 ^1H NMR ($\text{DMSO}-d_6$) δ 7.72-7.67 (m, 2 H), 7.45-7.29 (m, 4 H), 7.11-6.82 (m, 6 H), 6.51 (s, 1 H), 3.63-3.48 (m, 5 H), 2.92-2.88 (m, 1 H), 2.04-1.73 (m, 8 H), 1.65-1.59 (m, 1 H), 1.53-1.47 (m, 1 H), 1.01-0.97 (m, 6 H);
 MS m/z 683 ($M^+ - 1$, 100).

11870

Example 1086

N-[4-(N-(5-phenyl-(4-chlorophenyl)furan-2-ylmethyl-N-isopropylaminomethyl)-2-(2-methylphenyl)benzoyl]methionine, lithium salt

11875



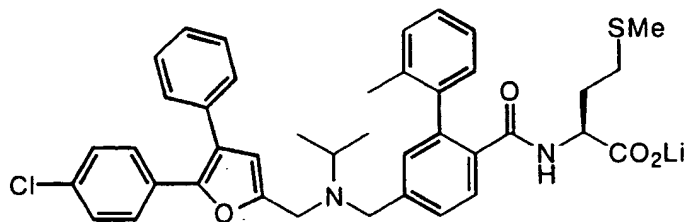
Example 1086A

N-[4-(N-(5-phenyl-(4-chlorophenyl)furan-2-ylmethyl-N-isopropylaminomethyl)-2-(2-methylphenyl)benzoyl]methionine, methyl ester

11880

To a solution of the bromo ester (60 mg, 0.086 mmol) in DME (5 mL) was added benzenboronic acid (21 mg, 0.17 mmol), CsF (39 mg, 0.26 mmol), and [1,1'-bis(diphenylphosphino)ferrocene]dichloropalladium(II), complex with dichloromethane (1:1) (7 mg, 0.009 mmol) and the resulting mixture heated to 80 °C overnight. The reaction was cooled and the reaction filtered through Celite, washing the bed with EtOAc. The filtrate was concentrated in vacuo and the residue purified by flash chromatography (hexane EtOAc 4:1) to give 31 mg (52%) of a yellow oil;
MS m/z 695 ($M^+ + 1$, 100).

11885



11890

Example 1086B

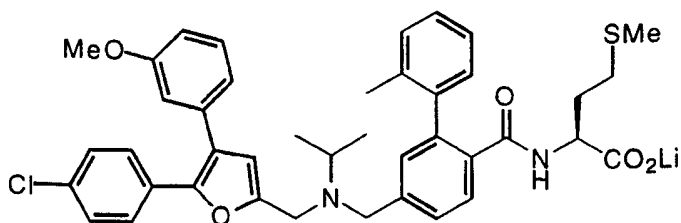
N-[4-(N-(5-phenyl-(4-chlorophenyl)furan-2-ylmethyl-N-isopropylaminomethyl)-2-(2-methylphenyl)benzoyl]methionine, lithium salt

The ester (30 mg, 0.04 mmol) was hydrolyzed as in example 1084 E to give 30 mg of a cream powder;

11895

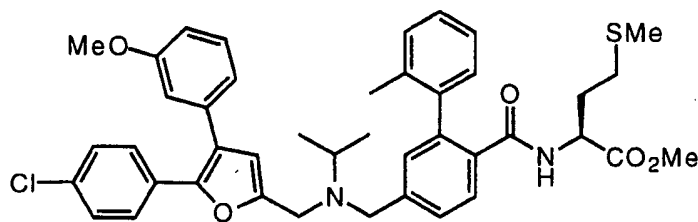
^1H NMR (DMSO- d_6) δ 7.47-6.85 (m, 17 H), 6.47 (s, 1 H), 3.73-3.58 (m, 5 H), 3.06-3.01 (m, 1 H), 2.11-1.77 (m, 8 H), 1.63-1.57 (m, 1 H), 1.51-1.43 (m, 1 H), 1.05-1.01 (m, 6 H);
MS m/z 679 ($M^+ - 1$, 100).

11900

Example 1087

N-[4-(N-(5-(3-methoxyphenyl)-(4-chlorophenyl)furan-2-yl)methyl)-N-isopropylaminomethyl]-2-(2-methylphenyl)benzoyl]methionine, lithium salt

11905

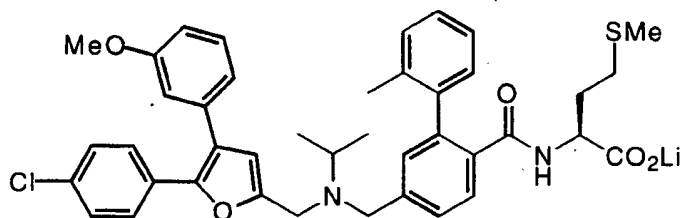
Example 1087A

N-[4-(N-(5-(3-methoxyphenyl)-(4-chlorophenyl)furan-2-yl)methyl)-N-isopropylaminomethyl]-2-(2-methylphenyl)benzoyl]methionine, methyl ester

11910

The bromo ester (62 mg, 0.088 mmol) was coupled to m-methoxybenzeneboronic acid as in example 1086 A. Flash chromatography (hexane/EtOAc 4:1) gave 38 mg (55%) of an oil;

MS m/z 725 ($M^+ + 1$, 100).



11915

Example 1087B

N-[4-(N-(5-(3-methoxyphenyl)-(4-chlorophenyl)furan-2-yl)methyl)-N-isopropylaminomethyl]-2-(2-methylphenyl)benzoyl]methionine, lithium salt

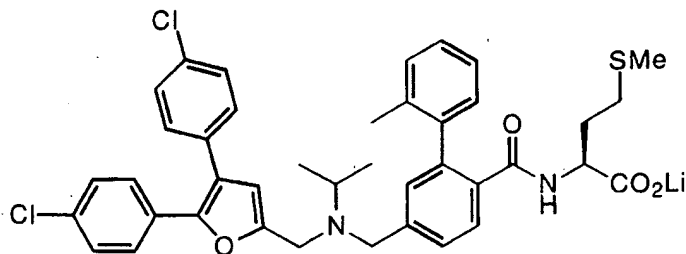
11920

The ester (38 mg, 0.054 mmol) was hydrolyzed as in example 1084 E to give 38 mg of a beige powder;

^1H NMR (DMSO- d_6) δ 7.69-7.02 (m, 12 H), 6.84-6.79 (m, 4 H), 6.42 (s, 1 H), 3.65-3.48 (m, 8 H), 2.97-2.93 (m, 1 H), 2.04-1.75 (m, 8 H), 1.63-1.57 (m, 1 H), 1.51-1.43 (m, 1 H), 1.03-0.98 (m, 6 H);

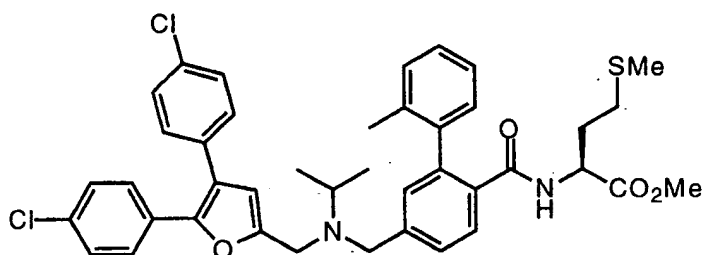
MS m/z 709 ($M^+ - 1$, 100).

11925

Example 1088

N-[4-(N-(4,5-di(4-chlorophenyl)furan-2-yl)methyl)-N-isopropylaminomethyl]-2-(2-methylphenyl)benzoyl]methionine, lithium salt

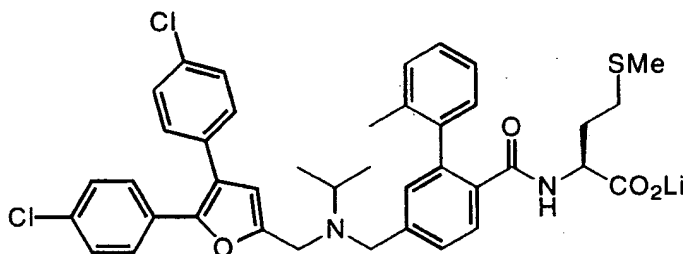
11930

Example 1088A

N-[4-(N-(4,5-di(4-chlorophenyl)furan-2-yl)methyl)-N-isopropylaminomethyl]-2-(2-methylphenyl)benzoyl]methionine, methyl ester

11935

The bromo ester (80 mg, 0.11 mmol) was coupled to p-chlorobenzenboronic acid as in example 1086 A. Flash chromatography (hexane/EtOAc 4:1) gave 38 mg (46 %) of an oil; MS m/z 729 ($M^+ + 1$, 100).

Example 1088B

N-[4-(N-(4,5-di(4-chlorophenyl)furan-2-yl)methyl)-N-isopropylaminomethyl]-2-(2-methylphenyl)benzoyl]methionine, lithium salt

11940

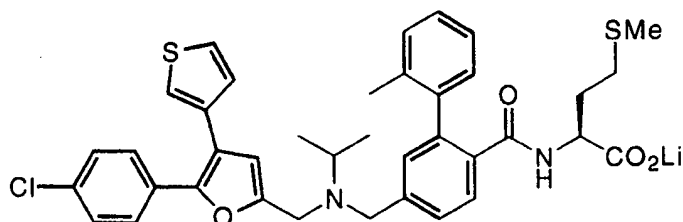
The ester (31 mg, 0.042 mmol) was hydrolyzed as in example 1084 E to give 31 mg of a cream powder;

11945

^1H NMR (DMSO- d_6) δ 7.47-7.29 (m, 11 H), 7.22-7.03 (m, 4 H), 6.89-6.87 (m, 1 H), 6.48 (s, 1 H), 3.73-3.62 (m, 5 H), 3.03-2.97 (m, 1 H), 2.08-1.83 (m, 8 H), 1.68-1.63 (m, 1 H), 1.57-1.51 (m, 1 H), 1.11-1.05 (m, 6 H);

MS m/z 713 ($M^+ - 1$, 100).

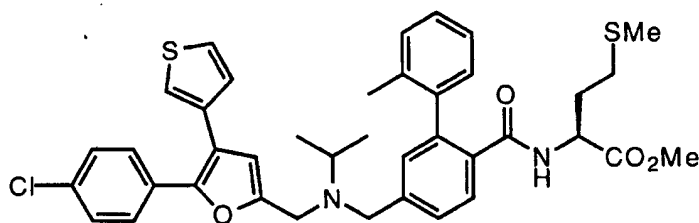
11950



Example 1089

N-[4-(N-(5-thien-3-yl-(4-chlorophenyl)furan-2-yl)methyl)-N-isopropylaminomethyl]-2-(2-methylphenyl)benzoyl]methionine, lithium salt

11955

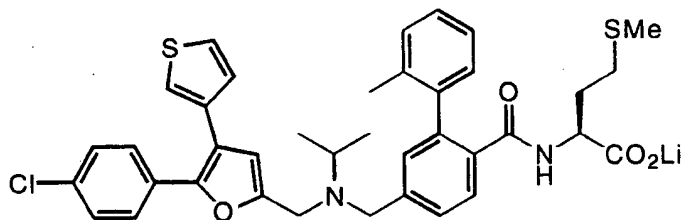


Example 1089A

N-[4-(N-(5-thien-3-yl-(4-chlorophenyl)furan-2-yl)methyl)-N-isopropylaminomethyl]-2-(2-methylphenyl)benzoyl]methionine, methyl ester

11960

The bromo ester (56 mg, 0.084 mmol) was coupled to 2-thiopheneboronic acid as in example 1086 A. Flash chromatography (hexane/EtOAc 4:1) gave 41 mg (73 %) of an oil; MS m/z 701 ($M^+ + 1$, 100).



11965

Example 1089B

N-[4-(N-(5-thien-3-yl-(4-chlorophenyl)furan-2-yl)methyl)-N-isopropylaminomethyl]-2-(2-methylphenyl)benzoyl]methionine, lithium salt

11970

The ester (38 mg, 0.054 mmol) was hydrolyzed as in example 1084 E to give 37 mg of a yellow powder;

^1H NMR (DMSO- d_6) δ 7.46-7.32 (m, 7 H), 7.11-6.99 (m, 7 H), 6.84-6.82 (m, 1 H), 6.43 (s, 1 H), 3.65-3.60 (m, 5 H), 2.96-2.92 (m, 1 H), 2.03-1.75 (m, 8 H), 1.63-1.58 (m, 1 H), 1.52-1.47 (m, 1 H), 1.02-0.99 (m, 6 H);